Docket No.: 025444.90400

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Ambrosio et al.

Patent No.: 5,829,434

Issued: November 3, 1998

For: Inhaler For Powdered Medications

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA
22313-1450

REQUEST FOR EXTENSION OF PATENT TERM UNDER
35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.701-1.791, this Request is being submitted by the Applicant, Schering Corporation ("Schering") with respect to the above-identified patent, namely U.S. Patent No. 5,829,434, which matured from application Serial No. 08/446,804, having a 35 U.S.C. §371 date of June 1, 1995. This application is a national phase application relating to International Application No. PCT/US93/12076, filed December 16, 1993, which is a continuation-in-part of Serial No. 07/992,959, filed December 18, 1992, now abandoned. Schering is the owner of the U.S. Patent No. 5,829,434 by virtue of the Assignment to Schering from the inventors, namely, Thomas J. Ambrosio, Charles R. Ashley, Alan J. Bilanin, Charles M. Huck, Andrew E. Kaufman, David J. Kenyon, Srinivas Manthena, Henry R. Sochon, Ken

Wilkinson and Tsong-Toh Yang (having executed the Assignment, respectively, on December 6, 1993, November 17, 1993, December 1, 1993, November 17, 1993, December 1, 1993, December 6, 1993, December 7, 1993, December 10, 1993, November 19, 1993 and December 6, 1993) of each of their interests in Serial No. 08/446,804. This Assignment has been recorded in the United States Patent and Trademark Office ("USPTO") on September 27, 1995, at Reel 007655, Frame 0784 and is attached hereto as Exhibit 1.

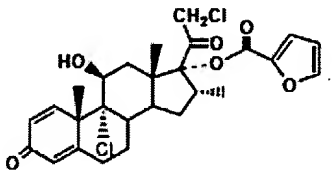
The following information is submitted in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.701 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740:

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is the ASMANEX® TWISTHALER® 220 mcg product, which is a cap-activated inhalation-driven multi-dose dry powder inhaler containing mometasone furoate and anhydrous lactose (which contains milk proteins). Each actuation of the ASMANEX® TWISTHALER® inhaler product provides a measured dose of 1.5 mg mometasone furoate inhalation powder, containing 220 mcg of mometasone furoate. This results in delivery of 200 mcg mometasone furoate from the mouthpiece, based on in vitro testing at flow rates of 30 L/min and 60 L/min with constant volume (2L). The amount of mometasone furoate emitted from the inhaler in vitro did not differ significantly for flow rates ranging from 28.3 L/min to 70 L/min for fixed intervals of 2 seconds. However, the amount of drug delivered to the lung will

depend on patient factors such as inspiratory flow and peak inspiratory flow through the device. In adult and adolescent patients with varied asthma severity, mean peak inspiratory flow rate through the device was 69 L/min (range 54-77/min).

Mometasone furoate, the active component in the ASMANEX® TWISTHALER® product, is a corticosteroid with the chemical name 9,21-dichloro-II(Beta),17-dihydroxy-16(alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) and the following chemical structure:



Mometasone furoate is a white powder with an empirical formula of C_{27} H_{30} Cl_2O_6, and molecular weight 521.44 Daltons. The approved label for the product is provided in Exhibit 2.

(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

The ASMANEX® TWISTHALER® product comprises a novel device that delivers a previously approved active ingredient, i.e., mometasone furoate. The regulatory review for the ASMANEX® TWISTHALER® product occurred under Section 505 of the FFDCA, 21 U.S.C. § 355.

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

The ASMANEX® TWISTHALER® product was approved by the FDA for commercial marketing on March 30, 2005 for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older, and for treatment of asthma patients who require oral corticosteroid therapy, where adding ASMANEX® TWISTHALER® therapy may reduce or eliminate the need for oral corticosteroids. See Exhibit 3 for a copy of the approval letter.

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED:

The ASMANEX® TWISTHALER® product comprises a novel device that delivers a previously approved active ingredient, i.e., mometasone furoate. The regulatory review for the ASMANEX® TWISTHALER® product occurred under Section 505 of the FFDCA, 21 U.S.C. § 355. The device component of the ASMANEX®

TWISTHALER® product has not been previously approved for commercial marketing or use under FFDCA, the Public Health Service Act. or the Virus-Serum-Toxin Act.

The active ingredient in the approved ASMANEX® TWISTHALER® product, namely mometasone furoate, was first approved for commercial marketing on April 30, 1987, in connection with approval under Section 505 of the FFDCA [21 U.S.C. §355] for the commercial marketing of ELOCON® Ointment, which contains mometasone furoate as its active ingredient, for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. (See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, searching under the Drug Name, ELOCON®.)

The active ingredient in the approved ASMANEX® TWISTHALER® product, namely mometasone furoate, was also approved for commercial marketing on October 1, 1997, in connection with approval under Section 505 of the FFDCA [21 U.S.C. §355] for the commercial marketing of NASONEX® Nasal Spray, which contains mometasone furoate monohydrate as its active ingredient, for the treatment of nasal symptoms of seasonal allergic and perennial rhinitis. (See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, searching under the Drug Name, NASONEX®.)

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SEC. 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

The ASMANEX® TWISTHALER® product was approved on March 30, 2005, and the last day within the sixty day period permitted for submission of an application for extension of the relevant U.S. Patent is May 31, 2005, (May 28, 2005 being a Saturday and May 30, 2005 being a statutory holiday, namely, Memorial Day). This application is being timely filed on May 27, 2005, before the expiration of the May 31, 2005 deadline.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO.: 5,829,434

INVENTORS: AMBROSIO, ET AL.

DATE OF ISSUE: NOVEMBER 3, 1998

EXPIRATION DATE: NOVEMBER 3, 2015

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

A copy of U.S. Patent No. 5,829,434 is attached as Exhibit 4.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No disclaimers were filed for U.S. Patent No. 5,829,434.

United States Patent No. 5,829,434 has not been re-examined and, as such, no re-examination certificate has been issued.

No certificates of correction have been filed for U.S. Patent No. 5,829,434.

The first maintenance fee for U.S. Patent No. 5,829,434 was paid on April 29, 2002 in good time, as shown by the Patent Bibliographic Data Sheet for this patent dated May 26, 2005, and the USPTO Maintenance Fee Statement dated May 26, 2005, both found in Exhibit 5.

The second and third maintenance fees for U.S. Patent No. 5,829,434 are not yet due. See the Maintenance Fees Window Dates document dated May 26, 2005, also found at Exhibit 5.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING THAT LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON:

(i) THE APPROVED PRODUCT, IF THE LISTED CLAIMS INCLUDE ANY CLAIM TO THE APPROVED PRODUCT;

(ii) THE METHOD OF USING THE APPROVED PRODUCT, IF THE LISTED CLAIMS INCLUDE ANY CLAIM TO THE METHOD OF USING THE APPROVED PRODUCT; AND

(iii) THE METHOD OF MANUFACTURING THE APPROVED PRODUCT, IF THE LISTED CLAIMS INCLUDE ANY CLAIM TO THE METHOD OF MANUFACTURING THE APPROVED PRODUCT.

U.S. Patent No. 5,829,434 claims the approved ASMANEX® TWISTHALER® product. At least claims 1, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26 and 27 read on the approved ASMANEX® TWISTHALER® product, literally or under the doctrine of equivalents. Upon request, Schering will provide models of the approved ASMANEX® TWISTHALER® product to the U.S. Patent and Trademark Office for examination in connection with this Request.

As shown in detail below, at least claim 1 of U.S. Patent No. 5,829,434 reads on the approved ASMANEX® TWISTHALER® product.

Claim 1 of U.S. Patent No. 5,829,434 reads as follows:

1. A powder inhaler comprising:

powder housing means for holding a supply of powdered material to be dispensed, said powder housing means including an inhalation conduit extending therethrough in a first direction, in displaced relation to said supply of powdered material;

metering plate means for holding a metered amount of said powdered material, said metering plate means including metered dose hole means for holding said metered amount of said powdered material, said metering plate means being positionable below said supply of powdered material, and said metering plate means and said powder housing means being relatively bi-

directionally rotatable with respect to each other about a common central axis so that said metered dose hole means can be placed in fluid communication selectively with said supply of powdered material or said inhalation conduit;

spring means for biasing said metering plate means and said powdered housing means toward each other to maintain contact therebetween;

rotation limiting means for restricting relative rotation between said powder housing means and said metering plate means to a predetermined angle;

counter means for providing a visual count of the number of doses of said powdered material that have been dispensed or remain to be dispensed in response to said relative rotation of said powder housing means and said metering plate means, said counter means including:

counter ring means for providing said visual count, said counter ring means being rotatable about said common central axis and having counting indicia thereon for displaying said visual count, and

actuating means for incrementally rotating said counter ring means in response to said relative rotation between said metering plate means and said powder housing means; and

display means through which one of said counting indicia from said counter ring means is displayed to indicate a count corresponding to a number of doses of powdered material that have been dispensed or remain to be dispensed.

The approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product (including various exploded views) is shown on Exhibit 6 to this Request.

Claim 1: Preamble

The approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product is a powder inhaler.

Claim 1: Powder Housing Means

The approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes a powder housing, shown on Exhibit 6 as Reservoir Sub-Assembly 2000-000C-8, which includes a chamber for holding a supply of powdered material (specifically, ASMANEX® brand mometsone furoate) as well as an inhalation conduit extending through Reservoir Sub-Assembly 2000-000C-8 and displaced in relation to the chamber holding the powdered material.

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the powder housing means of claim 1 includes, for example, powder housing 20 (e.g., FIG. 4), which includes powder conduit 60 (e.g., FIG. 5) which normally includes powder 62 (e.g., FIG. 4) for inhalation. As also shown and described in the specification, powder housing 20 also includes inhalation conduit 64 (e.g., FIG. 5), which extends through the powder housing 20 and is displaced in relation to the powder conduit 60. See, e.g., U.S. Patent No. 5,829,434, col. 10, line 23 - col. 11, line 45.

As shown on Exhibit 6, and as described above, the approved TWISTHALER® product includes the structures disclosed in the specification of U.S. Patent No. 5,829,434 corresponding to the powder housing element of claim 1, or equivalents of those structures. The powder-housing structures of the approved

TWISTHALER® product perform the same functions recited in claim 1 for the powder housing means, in substantially the same way, with substantially the same result. In the approved TWISTHALER® product, Reservoir Sub-Assembly 2000-000C-8 serves as powder housing means of claim 1.

Claim 1: Metering Plate Means

The approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes a metering plate, shown on Exhibit 6 as Dose Plate 0080-002C-8, which include a metered dose hole. As also shown on Exhibit 6, Dose Plate 0080-002C-8 is positioned below Reservoir Sub-Assembly 2000-000C-8. In the TWISTHALER® product, Dose Plate 0080-002C is stationary relative to Base 0010-000C-8; and Reservoir Sub-Assembly 2000-000C-8 bi-directionally rotates with respect to Dose Plate 0080-002C-8 about a common central axis so that the metered dose hole of Dose Plate 0080-002C-8 can be placed in fluid communication selectively with the supply of powdered material or the inhalation conduit of Reservoir Sub-Assembly 2000-000C-8.

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the metering plate includes, for example, metering dose plate 180 (e.g., FIG. 22), which includes dose hole 184. As described in the specification (e.g., col. 14, line 55 - col. 15, line 36), metering dose plate 180 and reservoir body 22 of powder housing 20 (e.g., FIG. 3) are relatively bi-directionally rotatable with respect to each other about a common central axis so that the metered dose hole 184 can be placed in fluid communication selectively with the supply of powdered material or the inhalation conduit 64.

As shown on Exhibit 6 and as discussed above, the approved TWISTHALER® product includes the structures disclosed in the specification of U.S.

Patent No. 5,829,434 corresponding to the metering plate means element of claim 1, or equivalents of those structures. The metering plate structures of the approved TWISTHALER® product perform the same functions recited in claim 1 for the metering plate means, in substantially the same way, with substantially the same result. In the approved TWISTHALER® product, Dose Plate 0080-002C-8 serves as metering plate means of claim 1.

Claim 1: Spring Means

The approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes a spring, shown on Exhibit 6 as Spring 0040-000N. As also shown on Exhibit 6, Spring 0040-000N is positioned with respect to Support Plate 0070-000C-8 and Retainer 0060-000C-8 to bias Dose Plate 0080-002C and Reservoir Sub-Assembly 2000-000C-8 towards each other in order to maintain contact between Dose Plate 0080-002C and Reservoir Sub-Assembly 2000-000C-8.

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the spring means includes, for example, spring 290 (e.g., FIG. 3), lower spring retainer 260 (e.g., FIG. 3) and support plate 300 (e.g., FIG. 3). As described in the specification (e.g., col. 16, line 21 - col. 17, line 9), these structures cooperate to bias the metering plate 180 and the powder housing 20 toward each other in order to maintain contact between the metering plate 180 and the powder housing 20.

As shown on Exhibit 6 and as discussed above, the approved TWISTHALER® product includes the structures disclosed in the specification of U.S. Patent No. 5,829,434 corresponding to the spring means element of claim 1, or equivalents of those structures. The spring structures of the approved TWISTHALER® product perform the same functions recited in claim 1 for the spring means, in substantially the same way, with substantially the same result. In the approved

TWISTHALER® product, Spring 0040-000N, Support Plate 0070-000C-8, and Retainer 0060-000C-8 serve as spring means of claim 1.

Claim 1: Rotation Limiting Means

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the rotation limiting means of claim 1 includes, for example, nub 163 and rotation limiting tab 162 (e.g., FIGs. 16 and 21) and stops 344 and 346 (e.g., FIGs. 42 and 44). As explained in the specification (col. 19, lines 36 - 46), accidental rotation of driving body 120 (e.g., FIG. 3) relative to adapter 320 (e.g., FIG. 3) is prevented by rotation limiting tab 162 stopping against stop 344 or stop 346. As explained in the specification (e.g., col. 12, line 46 - col. 15, line 36), driving body 120 drives rotation of powder housing 20. Adapter 320 is stationary relative to base 200 (e.g., FIG. 3) and metering does plate 180 (e.g., FIG. 3). Thus, prevention of accidental rotation of driving body 120 relative to adapter 320 also prevents accidental rotation of metering dose plate 180 relative to powder housing 20.

As shown in Exhibit 6, the approved TWISTHALER® product includes the structures disclosed in the specification of U.S. Patent No. 5,829,434 corresponding to the rotation limiting means element of claim 1, or equivalents of those structures. Body 0110-000C-8 of Upper Sub-Assembly 4000-000C-8 includes two downwardly extending tabs. These tabs fit into corresponding slots on the side of Adaptor 0150-000C-8, and prevent accidental rotation of Body 0110-000C-8 relative to Adaptor 0150-000C-8. As shown in Exhibit 6, Adaptor 0150-000C-8 is stationary relative to Base 0010-000C-8 and Dose Plate 0080-002C-8. Thus, the downwardly extending tabs on Body 0110-000C-8 cooperate with the corresponding slots in Adaptor 0150-000C-8 to limit relative rotation of the powder reservoir of Reservoir Sub-Assembly 2000-000C-8 and Dose Plate 0080-002C-8. These structures of the approved TWISTHALER® product perform

the same functions recited in claim 1 for the rotation limiting means, in substantially the same way, with substantially the same result. In the approved TWISTHALER® product, the downwardly extending tabs on Body 0110-000C-8 and the corresponding slots in Adaptor 0150-000C-8 serve as rotation limiting means.

Claim 1: Counter Means

The approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes a counter, including Int. Ctr. Ring [Intermittent Counter Ring] 0030-000C-8, Cont. Ctr. Ring [Continuous Counter Ring] 0020-000C-8, Pawl 0050-000C-8, pawl rotation stops protruding from Base 0010-000C-8, a display window in Adaptor 0150-000C-8, and a driving wall extending below Retainer 0060-000C-8, shown on Exhibit 6. The approved labeling for the ASMANEX® TWISTHALER® product (attached as Exhibit 2), and Exhibit 6 confirm that the counter of the approved TWISTHALER® product provides a visual count of the number of doses that remain to be dispensed in response to relative rotation of the Reservoir Sub-Assembly 2000-000C-8 (including the powder reservoir) and the Dose Plate 0080-002C-8.

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the counter means includes, for example, counter mechanism 580, including rotation prevention detents 224 and 232 on base 200 (e.g., FIG. 25); transparent plastic window 300 of adapter 320 (e.g., FIG. 40); continuous counter ring 590 and intermittent counter ring 620 (e.g., FIG. 3); pawl assembly 640 (e.g., FIG. 3); and pawl driving wall 274 of retainer 260 (e.g., FIGs. 30, 32 and 34). The specification explains how these structures cooperate to provide a visual count of the number of doses of powdered material that have been dispensed or remain to be dispensed in response to the relative rotation of the powder housing 20 and the metering plate 180. E.g., U.S. Patent 5,829,434, col. 25, line 26 - col. 28, line 20.

As shown on Exhibit 6 and as discussed above, the approved TWISTHALER® product includes the structures disclosed in the specification of U.S. Patent No. 5,829,434 corresponding to the counter means element of claim 1, or equivalents of those structures. The counter structures of the approved TWISTHALER® product perform the same functions recited in claim 1 for the counter means, in substantially the same way, with substantially the same result. In the approved TWISTHALER® product, Int. Ctr. Ring [Intermittent Counter Ring] 0030-000C-8, Cont. Ctr. Ring [Continuous Counter Ring] 0020-000C-8, Pawl 0050-000C-8, pawl rotation stops protruding from Base 0010-000C-8, a display window in Adaptor 0150-000C-8, and a driving wall extending below Retainer 0060-000C-8, serve as counter means of claim 1 of U.S. Patent No. 5,829,434.

Claim 1: Counter Ring Means

The counter means of claim 1 of U.S. Patent No. 5,829,434 includes, among other elements, counter ring means. As shown in Exhibit 6, the approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes counter rings, including Int. Ctr. Ring [Intermittent Counter Ring] 0030-000C-8, and Cont. Ctr. Ring [Continuous Counter Ring] 0020-000C-8. These rotate about a common central axis and have counting indicia for displaying the visual count of the number of doses that remain to be dispensed.

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the counter means includes, for example, continuous counter ring 590 and intermittent counter ring 620 (e.g., FIG. 3). The specification explains how these rings rotate about a common central axis and have counting indicia for displaying the number of doses of powdered material that have been dispensed or remain to be dispensed in

response to the relative rotation of the powder housing 20 and the metering plate 180. E.g., U.S. Patent 5,829,434, col. 25, line 26 - col. 28, line 20.

As shown on Exhibit 6 and as discussed above, the approved TWISTHALER® product includes the structures disclosed in the specification of U.S. Patent No. 5,829,434 corresponding to the counter ring means element of claim 1, or equivalents of those structures. The counter ring structures of the approved TWISTHALER® product perform the same functions recited in claim 1 for the counter ring means, in substantially the same way, with substantially the same result. In the approved TWISTHALER® product, Int. Ctr. Ring [Intermittent Counter Ring] 0030-000C-8, and Cont. Ctr. Ring [Continuous Counter Ring] 0020-000C-8 serve as counter ring means of claim 1 of U.S. Patent No. 5,829,434.

Claim 1: Actuating Means

The counter means of claim 1 of U.S. Patent No. 5,829,434 includes, among other elements, actuating means. As shown in Exhibit 6, the approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes Pawl 0050-000C-8 and pawl driving wall on the bottom of Retainer 0060-000C-8, with Pawl 0050-000C-8 engaged in the gear teeth on the inner circumferences of Int. Ctr. Ring [Intermittent Control Ring] 0030-000C-8 and of Cont. Ctr. Ring [Continuous Control Ring] 0020-000C-8. The pawl driving wall rotates with rotation of Retainer 0060-000C-8, which is part of and rotates with Reservoir Sub-Assembly 2000-000C-8, which also includes the powder reservoir. Since the Dose Plate 0080-002C-8 is stationary relative to Reservoir Sub-Assembly 2000-000C-8, the powder reservoir of the Reservoir Sub-Assembly 2000-000C-8 rotates relative to the Dose Plate 0080-002C-8. This relative rotation, coupled with the engagement of Pawl 0050-000C-8 with the gear

teeth of Int. Ctr. Ring [Intermittent Control Ring] 0030-000C-8 and of Cont. Ctr. Ring [Continuous Control Ring] 0020-000C-8, incrementally rotates these counter rings.

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the actuating means includes, for example, pawl assembly 640 (e.g., FIG. 3), gear teeth of continuous counter ring 590 (e.g., FIG. 3), gear teeth of intermittent counter ring 640 (e.g., FIG, 3), and pawl driving wall 274 (e.g., FIG. 32). The specification explains how these structures cooperate, in response to rotation of metering dose plate 180 relative to powder housing 20, to incrementally rotate the counter rings. E.g., U.S. Patent 5,829,434, col. 27, line 40 - col. 28, line 20.

As shown on Exhibit 6 and as discussed above, the approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes the structures disclosed in the specification of U.S. Patent No. 5,829,434 corresponding to the actuating means element of claim 1, or equivalents of those structures. The actuating structures of the approved TWISTHALER® product perform the same functions recited in claim 1 for the counter ring means, in substantially the same way, with substantially the same result. In the approved TWISTHALER® product, Pawl 0050-000C-8, pawl driving wall on the bottom of Retainer 0060-000C-8, gear teeth on the inner circumference of Int. Ctr. Ring [Intermittent Control Ring] 0030-000C-8, and gear teeth on the inner circumference of Cont. Ctr. Ring [Continuous Control Ring] 0020-000C-8 serve as actuating means of claim 1 of U.S. Patent No. 5,829,434.

Claim 1: Display Means

The counter means of claim 1 of U.S. Patent No. 5,829,434 includes, among other elements, display means. As shown in Exhibit 6, the approved TWISTHALER® component of the approved ASMANEX® TWISTHALER® product includes Adaptor 0150-00C-8, which includes a display window through which the

counting indicia of Int. Ctr. Ring [Intermittent Control Ring] 0030-000C-8 and of Cont. Ctr. Ring [Continuous Control Ring] 0020-000C-8 are displayed to indicate a count corresponding to a number of doses of powdered material (i.e., ASMANEX® mometasone furoate) that remain to be dispensed from the powder inhaler.

In the specification of U.S. Patent No. 5,829,434, structure corresponding to the display means includes, for example, window 330 of adapter 320 (e.g., FIG. 40). As explained in the specification, the indicia on the intermittent counter ring 620 and the continuous counter ring 590 show the number of doses remaining to be dispensed, and this number is displayed though window 330 of adapter 320. E.g., U.S. Patent 5,829,434, col. 29, line 5 - col. 30, line 14.

As shown on Exhibit 6 and as discussed above, the approved TWISTHALER® product includes the structures disclosed in the specification of U.S. Patent No. 5,829,434 corresponding to the display means element of claim 1, or equivalents of those structures. The display structures of the approved TWISTHALER® product perform the same functions recited in claim 1 for the display means, in substantially the same way, with substantially the same result. In the approved TWISTHALER® product, the display window in Adaptor 00150-000C-8 serves as display means of claim 1 of U.S. Patent No. 5,829,434.

Accordingly, claim 1 of U.S. Patent No. 5,829,434 reads on the approved ASMANEX® TWISTHALER® product, either literally or under the doctrine of equivalents.

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

As noted above, Schering Corporation ("Schering") of Kenilworth, New Jersey is the assignee of record of United States Patent No. 5,829,434 by virtue of the Assignment provided at Exhibit 1.

In furtherance of the need for an approved NDA, Schering, on September 13, 1994, submitted to the FDA an "Investigational New Drug Application" for mometasone furoate dry powder inhaler under Section 505 of the FFDCA for the purpose of conducting clinical studies to support the approval of a subsequent NDA for the use of the ASMANEX® TWISTHALER® product. A copy of this Schering letter is attached as Exhibit 7. By a letter dated September 16, 1994, the FDA acknowledged receipt of the IND on September 14, 1994 and assigned it IND No. 46216. A copy of this letter is attached as Exhibit 8. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i) as October 14, 1994, the effective date

of an investigational exemption, which is 30 days after the filing date of the Investigational New Drug Application. (See 21 C.F.R. §312.40(b).)

On November 30, 1998, Schering submitted to the FDA an original NDA for a mometasone furoate inhalation powder product for the treatment of asthma. A copy of this Schering letter transmitting the NDA is attached as Exhibit 9. FDA acknowledged receipt of the NDA telephonically, and assigned it NDA No. 21-067.

On March 30, 2005, FDA approved NDA 21-067 for use of the ASMANEX® TWISTHALER® product for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older, and also for the treatment asthma patients who require oral corticosteroid therapy, where adding ASMANEX® TWISTHALER® therapy may reduce or eliminate the need for oral corticosteroids. See Exhibit 3.

Thus, for purposes of determining the "testing phase" of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i), the "testing phase" began on October 14, 1994, the effective date of IND 46216, and ended on November 30, 1998, the date the NDA 21-067 was initially submitted by Schering for a mometasone furoate dry powder inhaler under Section 505 of the FFDCA. And, for purposes of determining the "approval phase" of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(ii), the "approval phase" began on November 30, 1998, the date the NDA 21-067 was initially submitted by Schering to the FDA and ended on March 30, 2005, the date on which the NDA 21-067 was approved by the FDA for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older, and for treatment of asthma patients who require oral corticosteroid therapy, where adding ASMANEX® TWISTHALER® therapy may reduce or eliminate the need for oral corticosteroids.

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY SCHERING, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

Please see attached Exhibit 10 for a chart that provides the chronology of significant activities undertaken by Schering during the "testing phase" of the regulatory review period.

Please see attached Exhibit 11 for a chart that provides the chronology of significant activities undertaken by Schering during the "approval phase" of the regulatory review period.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to the relevant version of 35 U.S.C. §154 applicable to U.S. Patent No. 5,829,434 and 35 U.S.C. §156, the term of U.S. Patent No. 5,829,434 is currently set to expire on November 3, 2015. This application is, therefore, being submitted prior to the expiration of the term of U.S. Patent No. 5,829,434.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Schering Corporation, the owner of record of U.S. Patent No. 5,829,434. Schering is the owner of record by virtue of the Assignments set forth in Exhibit 1, and discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on March 30, 2005, the date the product received permission for marketing under Section 505 of the FFDCA, and ending on May 31, 2005 (i.e., May 28, 2005 being a Saturday and May 30, 2005 being a statutory holiday, namely, Memorial Day). Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the March 30, 2005 letter from the FDA (Exhibit), to Schering Corporation, the product was subject to a regulatory review period under Section 505 of the FFDCA, 21 U.S.C. §355, before its commercial marketing or use.

(5) The ASMANEX® TWISTHALER® product comprises a novel device that delivers a previously approved active ingredient, i.e., mometasone furoate. The regulatory review for the ASMANEX® TWISTHALER® product occurred under Section 505 of the FFDCA, 21 U.S.C. § 355. The permission for the commercial marketing of the ASMANEX® TWISTHALER® product is the first permitted commercial marketing and use under Section 505 of the FFDCA, 21 U.S.C. §355, of the device component of the product. This is confirmed by the absence of any approved new device application for the device component of the ASMANEX® TWISTHALER® product prior to March 30, 2005.

(b) Statement as to length of extension claimed:

The 17 year from filing term of U.S. Patent No. 5,829,434 now expiring on November 3, 2015 should be extended to the statutory limit of March 30, 2019, in accordance with 35 U.S.C. §156(c)(3).

This extension was determined on the following basis. As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND 46216 of October 14, 1994 and the submission of the NDA 21-067 on November 30, 1998 (i.e., the "testing phase"), a period of 1,508 days, plus the length of time between the submission of the NDA 21-067 on November 30, 1998 to NDA approval on March 30, 2005 (i.e., the "approval phase"), a period of 2,312 days. These two periods added together equal 3,820 days.

Pursuant to the introduction of 35 U.S.C. §156(c), the term of the patent eligible for extension shall be extended only for that portion of the regulatory review period that occurs after the date the patent is issued. In this case, IND 46216 was pending for 1482 days before the issuance of U.S. Patent No. 5,829,434. Thus, the period calculated under §156(g)(1)(B)(i) is reduced, such that 26 days of the testing phase remain and 2,312 days remain in the approval phase of the regulatory period.

Section 156(c)(2) requires the period calculated under §156(g)(1)(B)(i) (i.e., the "testing phase") to be reduced by one-half of what is now the 26 day period; this reduction results in a value of 13 days.

From the foregoing calculation, an extension of 2,325 days results, i.e., the period under 35 U.S.C. 156(g)(1)(B)(i) (13 days) plus the period under 35 U.S.C. §156(g)(1)(B)(ii) (2,312 days). This length of an extension would theoretically provide a new expiry date for U.S. Patent No. 5,829,434 of March 16, 2022. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. In this case, since the current expiry date of U.S. Patent No. 5,829,434 is November 3, 2015, no patent term extension can extend the term of the patent beyond November 3, 2020. Consequently, this provision operates to limit the possible extension available to U.S. Patent 5,829,434.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term post approval date (i.e., March 30, 2005) exceeding 14 years after the date of approval, that is, March 30, 2019, the period of extension would be limited so that this period does not exceed 14 years. In this case, this provision also operates to limit the possible extension available to U.S. Patent 5,829,434.

Accordingly, United States Patent No. 5,829,434 is eligible for a patent term extension from November 3, 2015 to March 30, 2019.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. §1.765).

Schering acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE 37 C.F.R. §1.20(J)):

The Director is hereby authorized to charge our Deposit Account No. 50-0740, under Docket No. 025444.90400, in the amount of **$1,120.00**. The Director is also hereby authorized to charge our Deposit Account No. 50-0740, under Docket No. 025444.90400, with respect to any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

Paul J. Berman, Esq.
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
Telephone No.: (202) 662-6000
Facsimile No.: (202) 662-6291

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156 is accompanied by two additional copies of the Request, for a total submission of three copies.

The undersigned is authorized to act on behalf of the Applicant, Schering Corporation, by virtue of the executed Statement Under 37 C.F.R. 3.73(b) and the executed Power of Attorney and Correspondence Address Indication Form, both of which are attached to the original Request. Two additional copies of these papers also are being filed to accompany the two additional copies of the Request.

Dated: May 27, 2005

Respectfully submitted,

By _____

Natalie M. Derzko
Registration No.: 48,102
Paul J. Berman
Registration No.: 36,744
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000
Attorneys for Applicant

Exhibit 1

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 5829434 **Issue Dt:** 11/03/1998 **Application #:** 08446804 **Filing Dt:** 06/01/1995

Inventors: THOMAS J. AMBROSIO, CHARLES R. ASHLEY, ALAN J. BILANIN, CHARLES M. HUCK et al

Title: INHALER FOR POWDERED MEDICATIONS

Assignment: 1

Reel/Frame: 007655/0784 **Recorded:** 09/27/1995 **Pages:** 9

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors:	AMBROSIO, THOMAS J.	**Exec Dt:** 12/06/1993
	ASHLEY, CHARLES R.	**Exec Dt:** 11/17/1993
	BILANIN, ALAN J.	**Exec Dt:** 12/01/1993
	HUCK, CHARLES M.	**Exec Dt:** 11/17/1993
	KAUFMAN, ANDREW E.	**Exec Dt:** 12/01/1993
	KENYON, DAVID J.	**Exec Dt:** 12/06/1993
	MANTHENA, SRINIVAS	**Exec Dt:** 12/07/1993
	SOCHON, HENRY R.	**Exec Dt:** 12/10/1993
	WILKINSON, KEN	**Exec Dt:** 11/19/1993
	YANG, TSONG-TOH	**Exec Dt:** 12/06/1993

Assignee: SCHERING CORPORATION
2000 GALLOPING HILL ROAD
KENILWORTH, NEW JERSEY 07033

Correspondent: SCHERING-PLOUGH CORPORATION
ROBERT A. FRANKS
200 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

Search Results as of: 05/26/2005 06:09 PM

If you have any comments or questions concerning the data displayed, contact OPR / Assignments at 703-308-9723

10-19-1995

FORM PTO-1595
1-31-92

100078463

SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

PD03480

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents of copy thereof.

1. Name of conveying party(ies):

4. THOMAS J. AMBROSIO
CHARLES R. ASHLEY
3. ALAN J. BILANIN

MRD 9-29-95

Additional name(s) of conveying party(ies) attached? X Yes __No

2. Name and address of receiving party(ies):

Name: SCHERING CORPORATION

Internal Address: 2000 Galloping Hill Road

Kenilworth, New Jersey 07033-0530

Street Address: Same as Above.

City: _____ State: ____ ZIP: _____

Additional names(s) & address(es) attached? __ Yes X No

3. Nature of conveyance:

X Assignment ___ Merger

___ Security Agreement ___ Change of Name

___ Other _____

Execution Date: PLEASE SEE ATTACHED

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s): 08/446,804

B. Patent No.(s)

Additional numbers attached? ___ Yes X No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: ROBERT A. FRANKS

Internal Address: Patent Department, K-6-1 1990

Schering-Plough Corporation

Street Address: 2000 Galloping Hill Road

City: Kenilworth State: NJ ZIP: 07033-0530

6. Total number of applications and patents involved: (1)

7. Total fee (37 CFR 3.41): ..... $ 40.00

___ Enclosed

X Authorized to be charged to deposit account

8. Deposit account number:

19-0365

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

UM50087 10/06/95 08446804 19-0365 050 581 40.00CH

9. Statement and signature

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

ROBERT A. FRANKS
Name of Person Signing

Robert A. Franks
Signature

September 22, 1995
Date

Registration No. 28,605

Total number of pages including cover sheet, attachments and documents:

OMB No. 0551-0011 (exp 4/94)

FORM PTO-1595
RECORDATION FORM COVER SHEET
PATENT FORM COVER SHEET
PATENTS ONLY

1. Additional name(s) of conveying party(ies):
(continued from page 1)

4. CHARLES M. HUCK
5. ANDREW E. KAUFMAN
6. DAVID J. KENYON
7. SRINIVAS MANTHENA
8. HENRY R. SOCHON
9. KEN WILKINSON
10. TSONG-TOH YANG

2. Additional names(s) and address(es) of receiving party(ies):
(continued from page 1)

None.

3. Execution Date
(continued from page 1)

1. THOMAS J. AMBROSIO	DECEMBER 6, 1993
2. CHARLES R. ASHLEY	NOVEMBER 17, 1993
3. ALAN J. BILANIN	DECEMBER 1, 1993
4. CHARLES M. HUCK	NOVEMBER 17, 1993
5. ANDREW E. KAUFMAN	DECEMBER 1, 1993
6. DAVID J. KENYON	DECEMBER 6, 1993
7. SRINIVAS MANTHENA	DECEMBER 7, 1993
8. HENRY R. SOCHON	DECEMBER 10, 1993
9. KEN WILKINSON	NOVEMBER 19, 1993
10. TSONG-TOH YANG	DECEMBER 6, 1993

4. Additional application number(s) or registration number(s):
(continued from page 1)

A. Patent Application No.(s):

None.

B. Patent No.(s):

None.

FORM PTO-1595
RECORDATION FORM COVER SHEET
PATENT FORM COVER SHEET
PATENTS ONLY

1. Additional name(s) of conveying party(ies):
(continued from page 1)

4. CHARLES M. HUCK
5. ANDREW E. KAUFMAN
6. DAVID J. KENYON
7. SRINIVAS MANTHENA
8. HENRY R. SOCHON
9. KEN WILKINSON
10. TSONG-TOH YANG

2. Additional names(s) and address(es) of receiving party(ies):
(continued from page 1)

None.

3. Execution Date
(continued from page 1)

1. THOMAS J. AMBROSIO	DECEMBER 6, 1993
2. CHARLES R. ASHLEY	NOVEMBER 17, 1993
3. ALAN J. BILANIN	DECEMBER 1, 1993
4. CHARLES M. HUCK	NOVEMBER 17, 1993
5. ANDREW E. KAUFMAN	DECEMBER 1, 1993
6. DAVID J. KENYON	DECEMBER 6, 1993
7. SRINIVAS MANTHENA	DECEMBER 7, 1993
8. HENRY R. SOCHON	DECEMBER 10, 1993
9. KEN WILKINSON	NOVEMBER 19, 1993
10. TSONG-TOH YANG	DECEMBER 6, 1993

4. Additional application number(s) or registration number(s):
(continued from page 1)

A. Patent Application No.(s):

None.

B. Patent No.(s):

None.

ASSIGNMENT

For good and valuable consideration paid to us.

(1) Thomas J. Ambrosio (2) Charles R. Ashley
(3) Alan J. Bilanin (4) Charles M. Huck
(5) Andrew E. Kaufman (6) David J. Kenyon
(7) Srinivas Manthena (8) Henry R. Sochon
(9) Ken Wilkinson (10) Tsong-Toh Yang

of respectively,

(1) Somerville, New Jersey (2) Clinton, New Jersey
(3) Princeton, New Jersey (4) Gladstone, New Jersey
(5) Robbinsville, New Jersey (6) Morristown, New Jersey
(7) Bricktown, New Jersey (8) Clifton, New Jersey
(9) Round Lake, Illinois (10) Warren, New Jersey

by **SCHERING CORPORATION**, a corporation organized under the laws of the State of New Jersey, United States of America, having its principal office at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, United States of America, (hereinafter called "**SCHERING**"), we each do hereby sell, assign and set over unto said **SCHERING** each of our entire right, title and interest in all countries of the world in and to any and all of our inventions and discoveries in **INHALER FOR POWDERED MEDICATIONS**

as described and/or claimed in our International Application under the Patent Cooperation Treaty and subsequently* officially identified as International Patent Application Number PCT/US93/12076 filed on December 16, 1993 and, if applicable, our corresponding United States Application Serial No. 08/446,804 filed on June 1, 1995, in and to the right to file patent applications in the name of **SCHERING**, its designee, or in any or all of our names, at its election, on the aforesaid inventions and discoveries in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified International Patent Application and with all rights of priority in United States Patent Application No. 07/992,959 filed December 18, 1992; United States Patent Application No. _____ filed _____; and United States Patent Application No. _____ filed _____; under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement to which the United States now is or hereafter becomes a signatory, in and to any and all Letters Patent that issue on any of the aforesaid patent applications, and in and to any continuations, divisions, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **SCHERING**, its successors, assigns and other legal representatives, to the full ends of the terms for which a Letters Patent therefor may be granted, as fully and

Acknowledgement

State of New Jersey)
) s.s.
County of Union)

On this 6th day of December, 1993,
personally appeared before me Thomas J. Ambrosio
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal) EILEEN MARGARET RANKOSKY
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES SEPT. 9, 1998

Eileen M. Rankosky
NOTARY PUBLIC

Acknowledgement

State of New Jersey)
) s.s.
County of Somerset)

On this 17 day of Nov., 1993,
personally appeared before me Charles R. Ashley
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

PATRICIA STUMP
(Seal) NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Aug. 22, 1995

Patricia Stump
NOTARY PUBLIC

Acknowledgement

State of New Jersey)
) s.s.
County of Middlesex)

On this 1st day of DECEMBER, 1993,
personally appeared before me Alan J. Bilanin
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

MONICA C. CLARKSON
(Seal) NOTARY PUBLIC OF NEW JERSEY
My Commission Expires July 7, 1994

Monica C. Clarkson
NOTARY PUBLIC

Acknowledgement

State of New Jersey)
) s.s.
County of Somerset)

On this 17 day of Nov., 1993,
personally appeared before me Charles M. Huck
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

PATRICIA STUMP
(Seal) NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Aug. 22, 1995

Patricia Stump
NOTARY PUBLIC

13026-1

Executed this 10 day of December 19 93.

Henry R. Sochon L.S.

Henry R. Sochon

Executed this ___ day of _____, 19 93.

Ken Wilkinson L.S.

Ken Wilkinson

Executed this 19 day of NOVEMBER, 19 93.

Tsong-Toh Yang L.S.

Tsong-Toh Yang

Executed this 6th day of December 1993

entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

And we hereby covenant and agree that we will at any time, upon the request and at the expense of SCHERING, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, and Letters Patent and reissues, renewals and extensions thereof in SCHERING, its successors, assigns or other legal representatives, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and that we will, at any time, upon the request and the expense of SCHERING, execute any additional or divisional applications for patents for said inventions and discoveries, or any part or parts thereof, and applications for patents of confirmation, registration and importation based on said Letters Patent and on Letters Patent issuing from said additional or divisional applications and reissues, renewals and extensions therefor, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of SCHERING, its successors, assigns or other legal representatives.

*We hereby authorize SCHERING to insert in this instrument the International Patent Application Number and United States Application Serial Number, if applicable, and the filing dates of said applications when officially notified thereof.

Executed this 6th day of December, 1993.

Thomas J. Ambrosio L.S.

Executed this ____ day of _____, 1993.

Charles R. Ashley L.S.

Executed this 17 day of November, 1993.

Alan J. Bilanin L.S.

Executed this 1 day of Dec., 1993.

Charles M. Huck L.S.

Executed this 17th day of November, 1993.

Andrew E. Kaufman L.S.

Executed this 1st day of December, 1993.

David J. Kenyon L.S.

Executed this 6th day of December, 1993.

Srinivas Manthena L.S.

Executed this 7th day of December, 1993

Acknowledgement

State of New Jersey)
) s.s.
County of Middlesex)

On this 1ST day of DECEMBER, 1993,
personally appeared before me Andrew E. Kaufman
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal) ..MONICA C. CLARKSON
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires July 7, 1994

Monica C. Clarkson
NOTARY PUBLIC

Acknowledgement

State of New Jersey)
) s.s.
County of Union)

On this 6th day of December, 1993,
personally appeared before me David J. Kenyon
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)
EILEEN MARGARET RANKOSKY
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES SEPT. 9, 1998

Eileen M. Rankosky
NOTARY PUBLIC

Acknowledgement

State of New Jersey)
) s.s.
County of Union)

On this 7th day of December, 1993
personally appeared before me Srinivas Manthena
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal) EILEEN MARGARET RANKOSKY
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES SEPT. 9, 1998

Eileen M. Rankosky
NOTARY PUBLIC

Acknowledgement

State of New Jersey)
) s.s.
County of Passaic)

On this 10 day of December, 1993,
personally appeared before me Henry R. Sochon
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

DONNA SAGUI
(Seal) NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES OCT. 15, 1998

Donna D Sagui
NOTARY PUBLIC

13076 1

Acknowledgement

State of Illinois)
) s.s.
County of Lake)

On this 19th day of November, 19 93
personally appeared before me Ken Wilkinson
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal) "OFFICIAL SEAL"
Terry Schneider
Notary Public, State of Illinois
My Commission Expires 7/5/94

Terry Schneider
NOTARY PUBLIC

Acknowledgement

State of New Jersey)
) s.s.
County of Union)

On this 6th day of December, 19 93
personally appeared before me Tsong-Toh Yang
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)
EILEEN MARGARET RANKOSKY
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES SEPT. 9, 1998

Eileen M. Rankosky
NOTARY PUBLIC

Acknowledgement

State of NJ)
) s.s.
County of _____)

On this _____ day of _____, 19 __.
personally appeared before me _____
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)

_____
NOTARY PUBLIC

Acknowledgement

State of _____)
) s.s.
County of _____)

On this _____ day of _____, 19 __.
personally appeared before me _____
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)

_____
NOTARY PUBLIC

13026-1

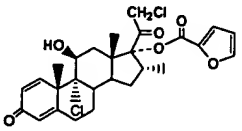
Exhibit 2

ASMANEX® TWISTHALER® 220 mcg
(mometasone furoate inhalation powder)

For Oral Inhalation Only

DESCRIPTION

Mometasone furoate, the active component of the ASMANEX® TWISTHALER® product, is a corticosteroid with the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16 (alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) and the following chemical structure:



Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}Cl_2O_6$, and molecular weight 521.44 Daltons.

The ASMANEX® TWISTHALER® 220 mcg product is a cap-activated inhalation-driven multi-dose dry powder inhaler containing mometasone furoate and anhydrous lactose (which contains milk proteins). Each actuation of the ASMANEX® TWISTHALER® 220 mcg inhaler provides a measured dose of 1.5 mg mometasone furoate inhalation powder, containing 220 mcg of mometasone furoate. This results in delivery of 200 mcg mometasone furoate from the mouthpiece, based on in vitro testing at flow rates of 30 L/min and 60 L/min with constant volume (2L). The amount of mometasone furoate emitted from the inhaler in vitro did not differ significantly for flow rates ranging from 28.3 L/min to 70 L/min for fixed intervals of 2 seconds. However, the amount of drug delivered to the lung will depend on patient factors such as inspiratory flow and peak inspiratory flow through the device. In adult and adolescent patients with varied asthma severity, mean peak inspiratory flow rate through the device was 69 L/min (range 54-77 L/min).

CLINICAL PHARMACOLOGY

Mechanism of Action

Mometasone furoate is a corticosteroid demonstrating potent antiinflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

In a three-way cross over study in 15 asthmatic patients receiving 50 or 100 mcg of mometasone furoate inhalation powder to placebo twice daily for two weeks, mometasone furoate inhalation powder reduced airway reactivity to adenosine monophosphate. In another study, pretreatment with mometasone furoate inhalation powder for 5 days attenuated the early and late phase reactions following inhaled allergen challenge and also reduced allergen-induced hyperresponsiveness to methacholine. Mometasone furoate inhalation powder was also shown to attenuate the increase in inflammatory cells (total and activated eosinophils) in induced sputum following allergen and methacholine challenge. The clinical significance of these findings is unknown.

Studies in asthmatic patients have demonstrated that ASMANEX® TWISTHALER® provides a favorable ratio of topical to systemic activity due to its primary local effect along with the extensive hepatic metabolism and the lack of active metabolites (see below).

Though effective for the treatment of asthma, glucocorticoids do not affect asthma symptoms immediately. Maximum improvement in symptoms following inhaled administration of mometasone furoate may not be achieved for 1 to 2 weeks or longer after starting treatment. When glucocorticoids are discontinued, asthma stability may persist for several days or longer.

Pharmacokinetics: Absorption: Following a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder to 6 healthy human subjects, plasma concentrations of unchanged mometasone furoate were shown to be very low compared to the total

radioactivity in plasma. Following an inhaled single 400 mcg dose of ASMANEX® TWISTHALER® treatment to 24 healthy subjects, plasma concentrations for most subjects were near or below the lower limit of quantitation for the assay (50 pcg/mL). The mean absolute systemic bioavailability of the above single inhaled 400 mcg dose, compared to an intravenous 400 mcg dose of mometasone furoate, was determined to be less than 1%. Following administration of the recommended highest inhaled dose (400 mcg twice daily) to 64 patients for 28 days, concentration-time profiles were discernible, but with large inter-subject variability. The coefficient of variation for Cmax and AUC ranged from approximately 50-100%. The mean peak plasma concentrations at steady state ranged from approximately 94 to 114 pcg/mL and the mean time to peak levels ranged from approximately 1.0 to 2.5 hours.

Distribution: Based on the study employing a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder in humans, no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an intravenous 400 mcg dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean terminal half-life of about 5 hours and the mean steady-state volume of distribution of 152 liters. The in vitro protein binding for mometasone furoate was reported to be 98 to 99% (in a concentration range of 5 to 500 ng/ml).

Metabolism: Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. In-vitro studies have confirmed the primary role of CYP 3A4 in the metabolism of this compound, however, no major metabolites were identified.

Excretion: Following an intravenous dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine.

Special Populations: Administration of a single inhaled dose of 400 mcg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pcg/ml). The observed peak plasma concentrations appear to increase with severity of hepatic impairment, however, the numbers of detectable levels were few. The effects of renal impairment, age or gender on mometasone furoate pharmacokinetics have not been adequately investigated.

Drug-Drug Interaction: An inhaled dose of mometasone furoate 400 mcg was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/ml on day 3 prior to co-administration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 (out of 12) subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/ml on Day 9 (211 to 324 pcg/ml). Since mometasone furoate plasma levels appear to increase and plasma cortisol levels appear to decrease upon concomitant administration of ketoconazole, caution should be exercised in the co-administration of these drugs.

Pharmacodynamics

The potential effect of mometasone furoate on the hypothalamic-pituitary-adrenal axis was assessed in a 29-day study. A total of 64 adult patients with mild to moderate asthma were randomized to one of 4 treatment groups: ASMANEX® TWISTHALER® 440 mcg twice daily, ASMANEX® TWISTHALER® 880 mcg twice daily, oral prednisone 10 mg once daily, or placebo. The 30-minute post-Cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 mcg/dl for the ASMANEX 440 mcg twice daily group and 20.8 mcg/dl for the ASMANEX 880 mcg twice daily group, compared to 14.5 mcg/dl for the oral prednisone 10 mg group and 25 mcg/dl for the placebo group. The difference between ASMANEX 880 mcg twice daily (twice the maximum recommended dose) and placebo was statistically significant.

Clinical Trials

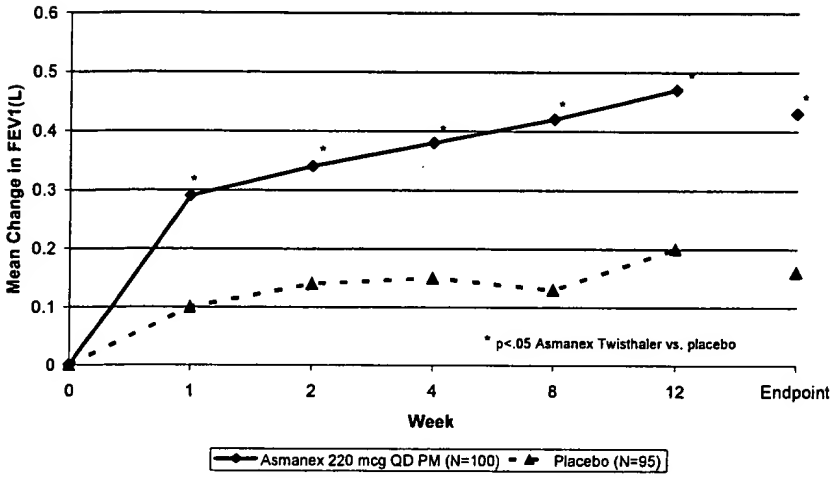
The efficacy of ASMANEX® TWISTHALER® has been studied across a wide range of doses in double-blind placebo-controlled 12-week treatment clinical trials involving 1941 patients 12 years of age and older with asthma of varying severity.

Patients Previously maintained on Bronchodilators Alone

ASMANEX® TWISTHALER® was studied in three 12-week double-blind trials in 737 patients with mild to moderate asthma (mean baseline FEV_1≐2.6 L, 72% of predicted normal) who were maintained on short-acting beta-2 agonists alone. The first two trials evaluated doses of 440 mcg administered as 2 inhalations once daily in the morning and one of these studies also evaluated 200 mcg twice-daily. In both trials, AM pre-dose FEV_1 was significantly improved at Endpoint (last observation) following treatment with 440 mcg ASMANEX® TWISTHALER® once daily in the morning as compared to placebo (14% vs. 2.5%, respectively in one trial and 16% vs. 5.5% in the other). There was also a significant improvement in AM pre-dose FEV_1 at Endpoint following treatment with ASMANEX® TWISTHALER® 220 mcg twice daily. Other measures of lung function (AM and PM PEFR) also showed improvement compared to placebo. Patients receiving ASMANEX® TWISTHALER® treatment had reduced frequency of beta-2 agonist rescue medication use compared to those on placebo (mean reductions at endpoint 2.2 and 0.5 puffs per day respectively from a baseline of 4.1 puffs/day). Additionally, fewer patients receiving ASMANEX® TWISTHALER® 440 mcg once daily experienced asthma worsenings than did patients receiving placebo.

In the third trial 195 asthmatic patients were treated with ASMANEX® TWISTHALER® 220 mcg once daily in the evening or placebo. The AM FEV_1 at Endpoint was significantly improved compared to placebo (mean change at endpoint 0.43L or 16.8% vs. 0.16L or 6% respectively, see Figure 1). Evening PEF increased 24.96L/min (7%) from baseline in the ASMANEX® TWISTHALER® group compared to 8.67 L/min (4%) in placebo.

Figure 1: A 12-Week Trial in Patients Previously Maintained on Inhaled Beta-2 Agonists



Patients Previously Maintained on Inhaled Corticosteroids

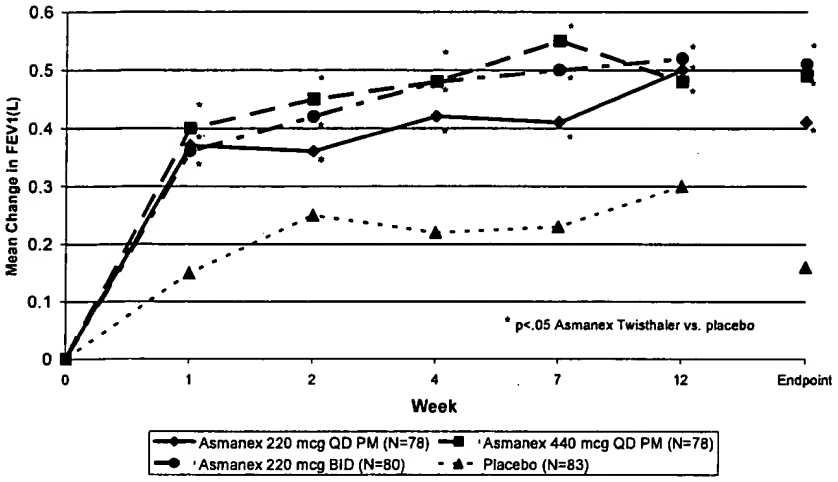
The efficacy and safety of ASMANEX® TWISTHALER® in doses ranging from 110 mcg twice daily to 440 mcg twice daily was evaluated in three trials in 1072 patients previously maintained on inhaled corticosteroids. In the first two trials, asthmatic patients (mean baseline FEV_1 ~ 2.6L, 76% predicted) were previously on either beclomethasone dipropionate [84-1200 mcg/day], flunisolide [100-2000 mcg/day], fluticasone propionate [110-880 mcg/day], or triamcinolone acetonide [300-2400 mcg/day]. The first trial included 307 patients who were treated in an open-label fashion with ASMANEX® TWISTHALER® 220 mcg (110 mcg x 2 inhalations) twice daily for 2 weeks followed by 12 weeks of double-blind treatment with ASMANEX® TWISTHALER® 440 mcg once daily in the morning or placebo. The second trial involved 365 patients who continued on their previous dose of inhaled corticosteroids during a 2-week screening period before being switched to ASMANEX® TWISTHALER® 440 mcg twice daily, 220 mcg twice daily, 110 mcg twice daily, beclomethasone dipropionate 168 mcg twice daily or placebo for 12 weeks.

In the first trial, AM pre-dose FEV_1 was effectively maintained (-1.4% change from baseline to Endpoint) over the 12 weeks in the patients who were randomized to ASMANEX® TWISTHALER® 440 mcg once daily in the morning while decreasing 10% at Endpoint in those switched to placebo. In addition, fewer patients treated with ASMANEX® TWISTHALER® experienced worsenings of asthma compared to placebo.

In the second trial, AM pre-dose FEV_1 was significantly increased at Endpoint when patients were switched to ASMANEX® TWISTHALER® 220 mcg twice daily (7% increase) or 440 mcg twice daily (6.2% increase) as compared to a decrease of 7% when switched to placebo. Additionally, beta-2 agonist rescue medication use was decreased for patients who received ASMANEX® TWISTHALER® treatment relative to those on placebo (mean reduction from baseline to Endpoint 1.1 puffs/day vs. increase of 0.7 puffs/day). Fewer patients receiving ASMANEX® TWISTHALER® treatment experienced asthma worsenings than did patients receiving placebo.

The third trial evaluated the efficacy and safety of ASMANEX® TWISTHALER® compared to placebo in 400 asthmatic patients (mean FEV_1 67% predicted at baseline) previously maintained on beclomethasone dipropionate (HFA or CFC) 168-600 mcg/day, budesonide 200-1200 mcg/day, flunisolide 500-2000 mcg/day, fluticasone propionate 88-880 mcg/day or triamcinolone acetonide 400-1600 mcg/day. Following a 28-day inhaled corticosteroid dose-reduction phase, patients were randomized to ASMANEX® TWISTHALER® 440 mcg once daily in the evening (QD PM), 220 mcg QD PM, 220 mcg twice daily or placebo. At Endpoint, patients who received ASMANEX® TWISTHALER® 220 mcg QD PM, 440 mcg QD PM, or 220 mcg twice daily had a significant improvement in AM FEV_1 [0.41L (19%), 0.49L (22%) and 0.51L (24%) in the 220 mcg QD PM, 440 mcg QD PM and 220 mcg twice daily treatment group respectively] compared to placebo [0.16L (8%)]. (See figure 2). Evening PEF increased 15.65 L/min (4.1%) with the 220 mcg QD PM dose, 39.26 L/min (10.7%) with the 440 mcg QD PM dose and 36.7 L/min (10.8%) with the 220 mcg twice daily dose respectively compared to a 1.4 L/min (1%) increase with placebo. Patients receiving all doses of ASMANEX® TWISTHALER® treatment had reduced frequency of beta agonist rescue medication use compared to those on placebo (mean reductions at endpoint of 1.4 to 1.8 puffs/day from a baseline of more than 3 puffs/day compared to an increase in use by 0.5 puffs/day for placebo). In addition, fewer patients receiving ASMANEX® TWISTHALER® experienced asthma worsenings than did those on placebo.

Figure 2: A 12-Week Trial in Patients Previously Maintained on Inhaled Corticosteroids



Patients Previously Maintained on Oral Corticosteroids

The efficacy of ASMANEX® TWISTHALER® 440 mcg and 880 mcg twice daily was evaluated in one 12-week double blind trial in patients previously maintained on oral corticosteroids. A total of 132 patients requiring oral prednisone (baseline mean daily oral prednisone requirement approximately 12 mg; baseline FEV_1 of 1.8L, 59% of predicted normal), most of whom were also on inhaled corticosteroids (baseline inhaled steroid: beclomethasone dipropionate [168-840 mcg/day], budesonide [800-1600 mcg/day], flunisolide [1000-2000 mcg/day], fluticasone propionate [440-1760 mcg/day], or triamcinolone acetonide [400-2400 mcg/day]) were studied. Patients who received ASMANEX® TWISTHALER® 440 mcg twice daily had a significant reduction in their oral prednisone (46%) as compared to placebo (164% increase in oral prednisone dose). Additionally, 40% of patients on ASMANEX 440 mcg twice daily were able to completely discontinue their use of prednisone, whereas 60% of patients on placebo had an increase in daily prednisone use. Patients on ASMANEX® TWISTHALER® had significant improvement in lung function (14% increase) compared to a 12% decrease in FEV_1 in the

placebo group. Additionally, mean rescue beta-2 agonist use was reduced to approximately 3 puffs/day from a baseline of 4-5 puffs/day with ASMANEX® TWISTHALER® treatment, compared to an increase of 0.3 puffs/day on placebo. Patients who received ASMANEX® TWISTHALER® 880 mcg twice daily experienced no additional benefit beyond that seen with 440 mcg twice daily.

INDICATIONS AND USAGE

ASMANEX® TWISTHALER® inhaler is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The ASMANEX® TWISTHALER® inhaler is also indicated for asthma patients who require oral corticosteroid therapy, where adding ASMANEX® TWISTHALER® therapy may reduce or eliminate the need for oral corticosteroids.

ASMANEX® TWISTHALER® is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

ASMANEX® TWISTHALER® therapy is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. Hypersensitivity to any of the ingredients of this preparation contraindicates its use (See DESCRIPTION).

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to the ASMANEX® TWISTHALER® inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although the ASMANEX® TWISTHALER® inhaler may improve control of asthma

symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity necessary for coping with these emergencies.

During periods of stress or severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe asthma attack (b) (4)

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ASMANEX® TWISTHALER®. Lung function (FEV1 or PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting and hypotension.

Transfer of patients from systemic corticosteroid therapy to the ASMANEX® TWISTHALER® inhaler may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases or who are not properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

The ASMANEX® TWISTHALER® inhaler is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with the

ASMANEX® TWISTHALER® inhaler, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with the ASMANEX® TWISTHALER® inhaler should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with the ASMANEX® TWISTHALER® inhaler. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

The ASMANEX® TWISTHALER® inhaler will often improve control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since mometasone furoate is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of the ASMANEX® TWISTHALER® inhaler in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing the ASMANEX® TWISTHALER® inhaler.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism, reduced bone mineral density and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, the ASMANEX® TWISTHALER® inhaler dose should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled glucocorticoids, including mometasone furoate. The clinical significance of small changes in bone mineral density with regard to long-term outcomes is

unknown. In a two-year double-blind study in 103 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (Baseline FEV_1 85-88% predicted), treatment with ASMANEX® TWISTHALER® 220 mcg twice daily resulted in significant reductions in lumbar spine (LS) BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.015 (-1.43%) for the ASMANEX® TWISTHALER® group compared to 0.002 (0.25%) for the placebo group. In another two year double blind study in 87 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilators therapy (Baseline FEV1 82-83% predicted), treatment with ASMANEX® TWISTHALER® 440 mcg twice daily demonstrated no statistically significant changes in lumbar spine BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.018 (-1.57%) for the ASMANEX® TWISTHALER® group compared to -0.006 (-0.43%) for the placebo group.

Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

Orally inhaled corticosteroids, including mometasone furoate inhalation powder, may cause a reduction in growth velocity when administered to pediatric patients. A reduction in growth velocity in children or teenagers may occur as a result of inadequate control of asthma or from use of corticosteroids for treatment. The potential effects of prolonged treatment on growth velocity should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including ASMANEX® TWISTHALER® each patient should be titrated to his/her lowest effective dose. (See **PRECAUTIONS, Pediatric Use** section)

Although patients in clinical trials have received the ASMANEX® TWISTHALER® inhaler on a continuous basis for periods of up to 2 years, the long-term local and systemic effects of ASMANEX® TWISTHALER® in human subjects are not completely known. In particular, the effects resulting from chronic use of the ASMANEX® TWISTHALER® inhaler on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with the ASMANEX® TWISTHALER® inhaler, localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral)

antifungal therapy while still continuing with ASMANEX® TWISTHALER® therapy, but at times therapy with the ASMANEX® TWISTHALER® inhaler may need to be temporarily interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Information for Patients: Patients being treated with the ASMANEX® TWISTHALER® inhaler should be given the following information. This information is intended to aid in the safe and effective use of the ASMANEX® TWISTHALER® inhaler. It is not a disclosure of all intended or possible adverse effects.

- Patients should be advised that ASMANEX® TWISTHALER® is not a bronchodilator and should not be used to relieve acute asthma (b) (4) --cute asthma symptoms should be treated with an inhaled, short-acting ---, such as albuterol. (b) (4)
- Patients should be advised to use the ASMANEX® TWISTHALER® inhaler at regular intervals since its effectiveness depends on regular use. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. If symptoms do not improve in that time frame or if the condition worsens, the patient should be instructed to contact the physician.
- Patients should be warned to avoid exposure to chickenpox or measles, and if they are exposed, to consult their physicians without delay.
- Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition.
- Patients should be advised that long-term use of inhaled corticosteroids, including ASMANEX® TWISTHALER® may increase the risk of some eye problems (cataracts or glaucoma).
- For the proper use of the ASMANEX® TWISTHALER® inhaler, and to attain maximum improvement, the patient should read and follow the accompanying Patient's Instructions for Use.

Patients should be instructed to record the date of pouch opening on the cap label, and discard the inhaler 45 days after opening the foil pouch or when the dose counter reads "00",

whichever comes first. The inhaler should be held upright while removing the cap. The medication should be taken as directed, breathing rapidly and deeply, and patients should not breathe out through the inhaler. The mouthpiece should be wiped dry and the cap replaced immediately following each inhalation, rotated fully until the click is heard. Rinsing of mouth after inhalation is advised. Patients should store the unit as instructed. The digital dose counter displays the doses remaining. When the counter indicates zero, the cap will lock and the unit must be discarded. Patients should be advised that if the dose counter is not working correctly, the unit should not be used and it should be brought to their physician or pharmacist.

Drug Interactions: In clinical studies, the concurrent administration of the ASMANEX® TWISTHALER® inhaler and other drugs commonly used in the treatment of asthma was not associated with any unusual adverse events. However, ketoconazole, a potent inhibitor of cytochrome P450 3A4, may increase plasma levels of mometasone furoate during concomitant dosing.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on an AUC basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 10 times the maximum recommended daily inhalation dose in adults on an AUC basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category*** **C**: When administered to pregnant mice, rats and rabbits, mometasone furoate increased fetal malformations. The doses that

produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) produced delays in ossification, but no malformations.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis). At 2800 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis).

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight and early pup survival. Similar effects were not observed at 7.5 mcg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on an AUC basis).

There are no adequate and well-controlled studies in pregnant women. ASMANEX® TWISTHALER® like other corticosteroids, should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. Experience with oral corticosteroids

since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

Nursing Mothers: It is not known if mometasone furoate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be used when ASMANEX® TWISTHALER® is administered to nursing women.

Pediatric Use: The safety and effectiveness of ASMANEX® TWISTHALER® treatment have been established in the age group 12 to 16 years. Clinical trials in adults and adolescents included 146 patients in this age group who received ASMANEX® TWISTHALER® treatment. No age-related differential responses to therapy were apparent. Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents (12 years of age and older) receiving orally inhaled corticosteroids, including ASMANEX® TWISTHALER® should be monitored routinely (e.g. via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including ASMANEX® TWISTHALER®, each patient should be titrated to his/her lowest effective dose.

Geriatric Use: A total of 175 patients 65 years of age and over (23 of whom were 75 years of age and over) have been treated with ASMANEX® TWISTHALER® in controlled clinical trials. No overall differences in safety or effectiveness were observed between these and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The following incidence of common adverse experiences is based on double-blind data from ten placebo-controlled clinical trials involving a total of 2809 patients previously maintained on inhaled steroids and/or bronchodilators (1140 males, 1669 females, age 12-83 years), who were treated for up to 12 weeks with the ASMANEX® TWISTHALER® product, an active comparator, or placebo. Adverse events were generally mild to moderate in severity.

Adverse Events with ≥3% Incidence in Controlled Clinical Trials with ASMANEX® TWISTHALER® in Patients Previously on Bronchodilators and/or Inhaled Corticosteroids

	(%) of Patients			
	MF DPI			
Adverse event	220 mcg BID (n=443)	440 mcg QD (n=497)	220 mcg QD PM (n=232)	Placebo (n=720)
Headache	22	17	20	20
Allergic Rhinitis	15	11	14	13
Pharyngitis	11	8	13	7
Upper Respiratory Inf.	10	8	15	7
Sinusitis	6	6	5	5
Candidiasis, oral	6	4	4	2
Dysmenorrhea[a]	9	4	4	4
Musculoskeletal Pain	8	4	4	5
Back Pain	6	3	3	4
Dyspepsia	5	3	3	3
Myalgia	3	2	3	2
Abdominal Pain	3	2	3	2
Nausea	3	1	3	2
Average Duration of Exposure (Days)	81	70	80	62

a: Percentages are based on the number of female patients.

The table above includes all events (whether considered drug-related or non-drug related by the investigators) that occurred at a rate of ≥3% in any one mometasone furoate group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for ASMANEX® TWISTHALER® patients should be taken into account.

The following other adverse events occurred in these clinical trials with an incidence of at least 1% but less than 3% and were more common on ASMANEX® TWISTHALER® therapy than on placebo:

Body as a Whole: fatigue, flu-like symptoms, accidental injury, pain, post-procedure pain
Gastrointestinal: flatulence, gastroenteritis, vomiting, anorexia
Hearing, vestibular: earache
Psychiatric: Insomnia
Reproductive, female: menstrual disorder
Resistance Mechanism: infection
Respiratory: dysphonia, epistaxis, nasal irritation, respiratory disorder, throat dry
Skin and Appendages: insect bite, skin laceration
Urinary: urinary tract infection

In a 12 week trial in adult asthmatics who previously required oral corticosteroids, the effects of ASMANEX® TWISTHALER® therapy administered as two 220 mcg inhalations twice daily (N=46) were compared with those of placebo (N=43). Adverse events, whether considered drug related or not by the investigators, reported in more than 3 patients in the ASMANEX® TWISTHALER® treatment group, and which occurred more frequently than on placebo were (ASMANEX® TWISTHALER® % vs. placebo %): musculoskeletal pain (22 vs. 14%), oral candidiasis (22 vs. 9%), sinusitis (22 vs. 19%), allergic rhinitis (20 vs. 5%), upper respiratory infection (15 vs. 14%), arthralgia (13 vs. 7%), fatigue (13 vs. 2%), depression (11 vs. 0%), and sinus congestion (9 vs. 0%). In considering these data, an increased duration of exposure for patients on ASMANEX® TWISTHALER® treatment (77 days vs. 58 days on placebo) should be taken into account.

Cases of growth suppression and decreased bone mineral density have been reported for orally inhaled corticosteroids, including mometasone furoate inhalation powder.

OVERDOSAGE

The potential for acute toxic effects following overdose with the ASMANEX® TWISTHALER® inhaler is low. Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical studies, overdose is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur. Single daily doses as high as 1200 mcg per day for 28 days were well-tolerated and did not cause a significant reduction in plasma cortisol AUC (94% of placebo AUC). Single oral doses up to 8000 mcg have been studied on human volunteers with no adverse events reported.

DOSAGE AND ADMINISTRATION

The ASMANEX® TWISTHALER® product should be administered by the orally inhaled route in patients 12 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer. The safety and efficacy of ASMANEX® TWISTHALER® when administered in excess of recommended doses have not been established.

The recommended starting doses and highest recommended daily dose for ASMANEX® TWISTHALER® treatment based on prior asthma therapy are provided in the table below.

Recommended Dosages for ASMANEX® TWISTHALER® Treatment

Previous Therapy	Recommended Starting Dose	Highest recommended daily dose
Bronchodilators alone	220 mcg QD PM *	440 mcg**
Inhaled corticosteroids	220 mcg QD PM *	440 mcg**
Oral corticosteroids †	440 mcg BID	880 mcg

* When administered once daily ASMANEX® TWISTHALER® should only be taken in the PM.
** The 440 mcg daily dose may be administered in divided doses of 220 mcg twice daily or as 440 mcg once daily.

NOTE: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

† For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:
Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of ASMANEX® TWISTHALER® therapy. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of mometasone furoate should be reduced to the lowest effective dosage.

Patients should be instructed to inhale rapidly and deeply (see enclosed patient instructions). Rinsing the mouth after inhalation is advised.

HOW SUPPLIED

The ASMANEX® TWISTHALER® product is comprised of an assembled plastic cap-activated dosing mechanism with dose counter, drug-product storage unit, drug-product formulation (240 mg), and mouthpiece, covered by a white screw cap which bears the product label. The body of the inhaler is white and the turning grip is pink with a clear plastic window indicating the number of doses remaining. The inhaler will not deliver subsequent doses once the counter reaches zero ("00").

The ASMANEX® TWISTHALER® product is available as:

ASMANEX® TWISTHALER® 220 mcg, which delivers 200 mcg mometasone furoate from the mouthpiece: 14 inhalation units (Institutional Use Only; NDC# 0085-1341-04); 30 inhalation units (NDC# 0085-1341-03); 60 inhalation units (For more than one inhalation daily; NDC # 0085-1341-02); or 120 inhalation units (For more than 2 inhalations daily; NDC # 0085-1341-01).

Each inhaler is supplied in a protective foil pouch with Patient's Instructions for Use.

Store in a dry place at 25°C (77°F); excursions permitted to 15-30°C (59-86° F) [see USP Controlled Room Temperature].

Discard the inhaler 45 days after opening the foil pouch or when dose counter reads "00", whichever comes first.

PATIENT'S INSTRUCTIONS FOR USE

ASMANEX®
TWISTHALER® 220 mcg
(mometasone furoate inhalation powder)
FOR ORAL INHALATION ONLY

Please read this leaflet carefully before taking ASMANEX® TWISTHALER®.
This leaflet does not contain the complete information about this medication. If you have any questions about ASMANEX® TWISTHALER®, ask your healthcare provider or pharmacist.

IMPORTANT POINTS TO REMEMBER ABOUT ASMANEX® TWISTHALER®

- Your healthcare provider has prescribed ASMANEX® TWISTHALER®. It contains a medication called mometasone furoate, which is a synthetic corticosteroid. This medication is used as maintenance treatment that helps prevent and control asthma symptoms.

- ASMANEX® TWISTHALER® is not a bronchodilator. You should not use ASMANEX® TWISTHALER® when you are having sudden symptoms of shortness of breath. Use an inhaled

short-acting bronchodilator such as albuterol to relieve sudden symptoms of shortness of breath.

- Your healthcare provider may prescribe bronchodilators such as albuterol for emergency relief if an acute asthma attack occurs.

- The inhaler delivers your medication as a very fine powder that you may (b) (4)------- mell or feel. ----------Whether or not you are able to sense (b) (4)---- f a dose, (b) (4) ---- not take extra ---------- ess your healthcare provider has told you to.

- Use the inhaler regularly and at the same time each day as prescribed by your healthcare provider. Maximum benefit may not be achieved for 1 to 2 weeks or longer. If your symptoms do not improve in that time frame or if your condition worsens, contact your healthcare provider.

Do not use the inhaler if you notice that it is not working correctly. Take it to your healthcare provider or pharmacist.

HOW TO USE

Remove the ASMANEX® TWISTHALER® from its foil pouch and write the date on the cap label. It's important to throw

away the inhaler 45 days after this date or when the dose counter reads "00", whichever comes first.

Step 1. Open inhaler
Hold the inhaler straight up with the pink portion (the base) on the bottom (Figure 1). It is important that you remove the cap of the TWISTHALER® while it is in this upright position to make sure that you get the right amount of medicine with each dose.

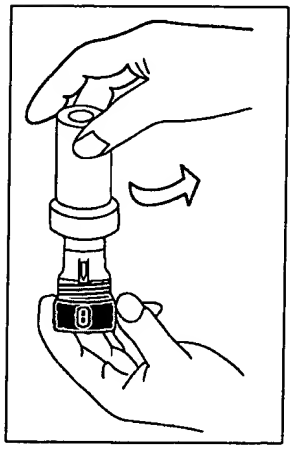


Figure 1 – Cap removal

Holding the pink base, twist the cap in a counter-clockwise direction to remove it. As you lift off the cap, the dose counter on the base will count down by one. (If you began with the dose counter reading "30," this action will cause it to now read "29.") This action loads the device with the medicine that you are now ready to inhale.

IT IS IMPORTANT TO

NOTE that the indented arrow (located on the white portion of the TWISTHALER®, directly above the pink base) is pointing to the dose counter (Figure 2).

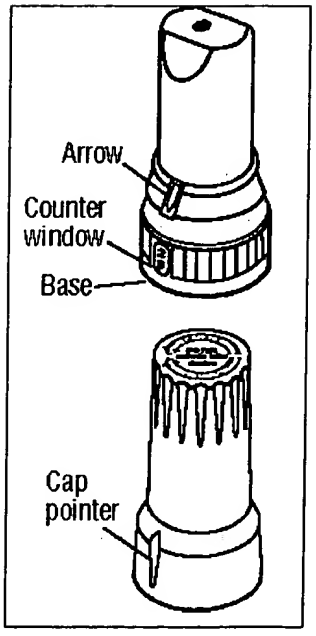


Figure 2

Step 2. Inhale dose
Exhale fully. Then bring the TWISTHALER®
up to your mouth with the mouthpiece
facing toward you. Place it in your mouth, holding it in a horizontal position as illustrated (Figure 3).
Firmly closing

your lips around the mouthpiece, take in a fast, deep breath. Since the medication is a very fine powder, you may not be able to feel or taste it after inhalation.

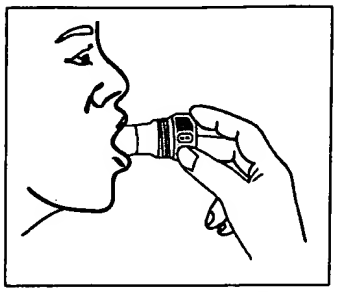


Figure 3 – Inhalation

Remove the TWISTHALER® from your mouth and hold your breath for about 10 seconds, or as long as you comfortably can.

IMPORTANT: DO NOT BREATHE OUT THROUGH THE INHALER.

After you take your medicine, it is important that you wipe the mouthpiece dry, if necessary, and immediately replace the cap, firmly closing the TWISTHALER® (Figures 4 and 5).

This is the only way to be sure that your next dose is properly loaded. Be sure that the arrow is in line with the dose-counter window. The cap needs to be put back on and turned in a clockwise direction, as you gently press down. You'll hear a distinctive "click" to let you know that the cap is fully closed.

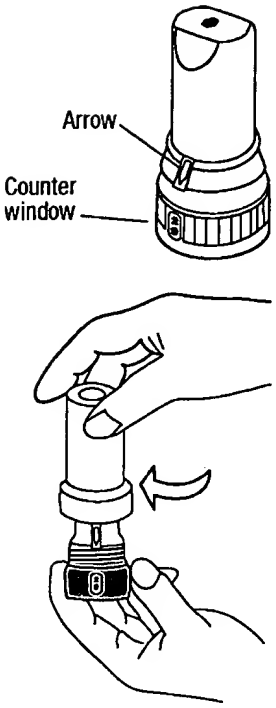


Figure 4 – Closing the inhaler

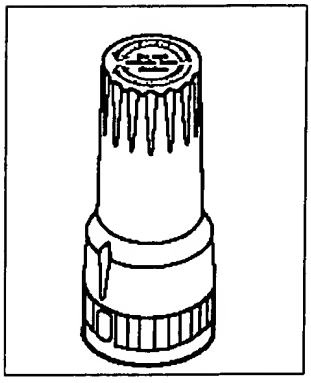


Figure 5 - Closed Inhaler

IT IS IMPORTANT TO REPEAT STEPS 1 AND 2 EACH TIME YOU INHALE.

Rinse your mouth after using.

STORING YOUR INHALER

Keep your inhaler clean and dry at all times. If the device needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed. Do not wash the inhaler. Avoid contact with any liquids.

Store in a dry place at 25°C (77F°); excursions permitted to 15-30°C (59-86°F)

Keep your inhaler out of the reach of young children.

HOW TO KNOW WHEN YOUR INHALER IS EMPTY

The inhaler has a dose indicator window on the pink base. It is a dose counter which displays the number of doses remaining. When the unit reads 01, this indicates the last remaining dose. After dose 01, the counter will read 00, and the cap will lock. The unit must then be discarded.

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. XX/XX 00000000

Exhibit 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-067

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Michael Belman
Associate Director and Liaison, Global Regulatory Affairs

Dear Mr. Belman:

Please refer to your new drug application (NDA) dated November 30, 1998, received December 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asmanex® Twisthaler® 220mcg (mometasone furoate inhalation powder).

We acknowledge receipt of your submissions dated September 29, November 15, and December 14, 2004, and February 1 and March 17, 2005.

The September 29, 2004, submission constituted a complete response to our May 17, 2004, action letter.

This new drug application provides for the use of Asmanex® Twisthaler® 220mcg (mometasone furoate inhalation powder) for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older and treatment of asthma patients who require oral corticosteroid therapy, where adding Asmanex® Twisthaler® therapy may reduce or eliminate the need for oral corticosteroids.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

The final printed labeling (FPL) must be identical to, except for including the revisions indicated, the enclosed labeling (text for the package insert, text for Patient's Instructions for Use) and submitted labeling (immediate container and carton labels submitted November 15, 2004). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-067.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 to 3 years and deferring pediatric studies for ages 4 to 11 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required post-marketing study commitments. The status of these post-marketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study (ies) under PREA for the maintenance treatment of asthma as prophylactic therapy in patients 4 to 11 years of age.

   Final Report Submission: April 1, 2007

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric post-marketing study commitment must be clearly designated "**Required Pediatric Study Commitments.**"

Submit clinical protocols to your IND for this product. Submit non-clinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these post-marketing study commitments must be prominently labeled "**Post-marketing Study Protocol**", "**Post-marketing Study Final Report,**" or "**Post-marketing Study Correspondence**."

We remind you of the agreements made in your submission dated February 1, 2005. These agreements are listed below.

1. Submit a prior approval supplement containing all pertinent supportive documentation for (b) (4) (b) (4)---------- for the drug product.

2. Re-evaluate the (b) (4)---------- acceptance criteria after one year of commercial exp---------

3. Re-evaluate the specifications for resistance to flow-by pressure drop after one year of commercial production experience.

4. Commence within three (3) months of approval, post-approval studies to determine the underlying factors leading to the shift in the (b) (4)---------- stage grouping deposition that is seen when comparing batches prepared (b) (4)---------- in 2002 with those recently made in 2004, i.e., increase in Group I and decrease in Group II and III deposition. You agree to a projected completion date of no more than twelve (12) months.

5. Submit three copies of an updated methods validation package containing the following information: a). composition of the drug product formulation; b). acceptance criteria and methods for the drug substance; c). acceptance criteria and methods for the drug product; d). supporting validation data for drug substance and drug product methods; e). a list of available samples with their respective sample numbers; f). analytical results for available samples. It is requested that these be submitted within a reasonably short time after approval (e.g., within 3 months).

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products, HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
3/30/05 03:56:59 PM

Exhibit 4

US005829434A

United States Patent [19]

Ambrosio et al.

[11] Patent Number: 5,829,434

[45] Date of Patent: Nov. 3, 1998

[54] **INHALER FOR POWDERED MEDICATIONS**

[75] Inventors: **Thomas J. Ambrosio**, Somerville; **Charles R. Ashley**, Clinton; **Alan J. Bilanin**, Princeton; **Charles M. Huck**, Gladstone; **Andrew E. Kaufman**, Robbinsville; **David J. Kenyon**, Morristown; **Srinivas Manthena**, Bricktown; **Henry R. Sochon**, Clifton, all of N.J.; **Ken Wilkinson**, Round Lake, Ill.; **Tsong-Toh Yang**, Warren, N.J.

[73] Assignee: **Schering Corporation**, Kenilworth, N.J.

[21] Appl. No.: **446,804**

[22] PCT Filed: **Dec. 16, 1993**

[86] PCT No.: **PCT/US93/12076**

§ 371 Date: **Jun. 1, 1995**

§ 102(e) Date: **Jun. 1, 1995**

[87] PCT Pub. No.: **WO94/14492**

PCT Pub. Date: **Jul. 7, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 992,959, Dec. 18, 1992, abandoned.

[51] **Int. Cl.**[6] **A61M 15/00**

[52] **U.S. Cl.** **128/203.15**; 128/200.18; 128/203.12

[58] **Field of Search** 128/203.15, 203.12, 128/203.18, 203.19, 203.21, 203.22, 203.23, 203.24; 222/390, 368, 321

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,596,370	5/1952	Bush	235/134
3,085,745	4/1963	Auberger	235/94

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

0069715	1/1983	European Pat. Off. .
0237507	9/1987	European Pat. Off. .
0451745	10/1991	European Pat. Off. .
0488609	6/1992	European Pat. Off. .
0505321	9/1992	European Pat. Off. .
0518087	12/1992	European Pat. Off. .
2022212	7/1970	France .
2041763	9/1980	United Kingdom .
1290484	9/1992	United Kingdom .
8605991	10/1986	WIPO .
9112040	8/1991	WIPO .
9204928	4/1992	WIPO .
9300123	1/1993	WIPO .
9309832	5/1993	WIPO .

Primary Examiner—John G. Weiss
Assistant Examiner—V. Srivastava
Attorney, Agent, or Firm—Robert A. Franks

[57] **ABSTRACT**

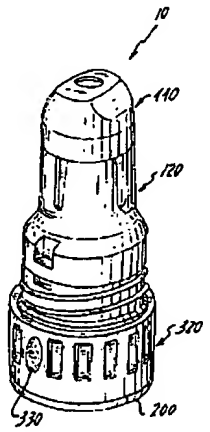
A powder inhaler comprising:

a powder housing for holding a supply of powdered material to be dispensed and a metering plate for holding a metered amount of said powdered material, the metering plate being alternately positionable below said supply of powdered material or within an inhalation conduit, by means of a bi-directional, angle-limited relative rotation about a common central axis;

a counter for providing a visual count of the number of doses of said powdered material that have been dispensed or remain to be dispensed in response to the relative rotation, the counter including: a continuous counter ring and a coaxially mounted intermittent counter ring, both rings being mounted on a base in surrounding relation to a retaining post, being rotatable about the common central axis and having counting indicia thereon for displaying said visual count; and

a display means through which at least one of the counting indicia is displayed to indicate a count corresponding to a number of doses of powdered material that have been dispensed or remain to be dispensed.

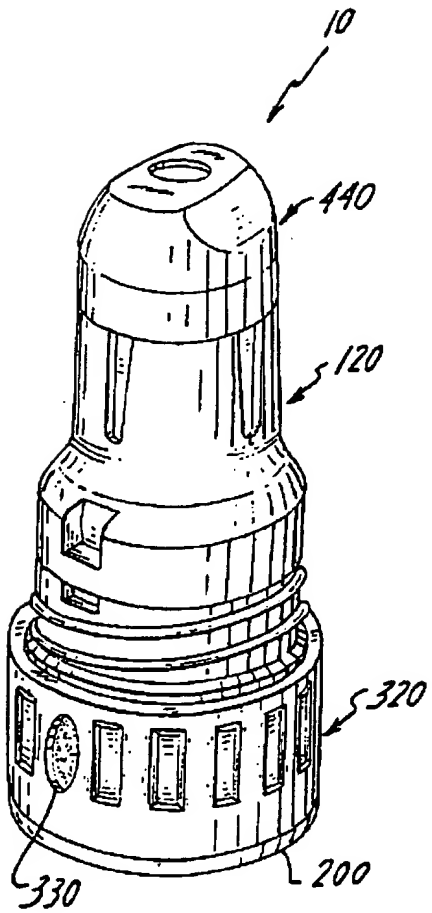
27 Claims, 23 Drawing Sheets



U.S. PATENT DOCUMENTS

3,655,952	4/1972	Johnson et al.	235/94 R
3,991,761	11/1976	Cocozza	128/266
4,069,819	1/1978	Valentini et al.	128/206
4,188,984	2/1980	Lyall	141/12
4,240,418	12/1980	Rosskamp et al.	128/203.15
4,452,239	6/1984	Malem	128/200.17
4,524,769	6/1985	Wetterlin	128/203.15
4,534,345	8/1985	Wetterlin	128/203.15
4,565,302	1/1986	Pfeiffer et al.	222/38
4,570,630	2/1986	Elliott et al.	128/203.15
4,667,668	5/1987	Wetterlin	128/203.15
4,668,218	5/1987	Virtunen	604/58
4,805,811	2/1989	Wetterlin	222/337
4,817,822	4/1989	Rand et al.	222/38
4,841,964	6/1989	Hurka et al.	128/203.15
4,860,740	8/1989	Kirk et al.	128/203.15
4,907,583	3/1990	Wetterlin et al.	128/203.15
4,989,763	2/1991	Brunet	222/635
5,033,463	7/1991	Cocozza	128/203.21
5,069,204	12/1991	Smith et al.	128/200.23
5,161,524	11/1992	Evans	128/203.15
5,243,970	9/1993	Ambrosio et al.	128/203.15
5,263,475	11/1993	Altermatt et al.	128/203.15
5,687,710	11/1997	Ambrosio et al.	128/203.15

FIG.2



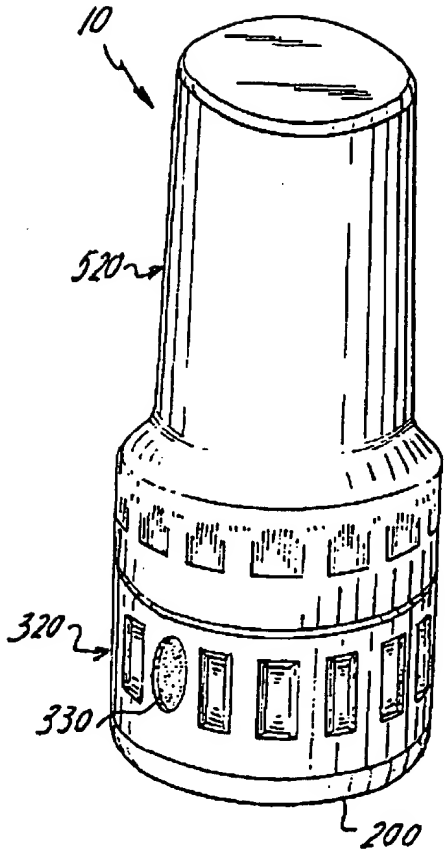


FIG.1

FIG. 3

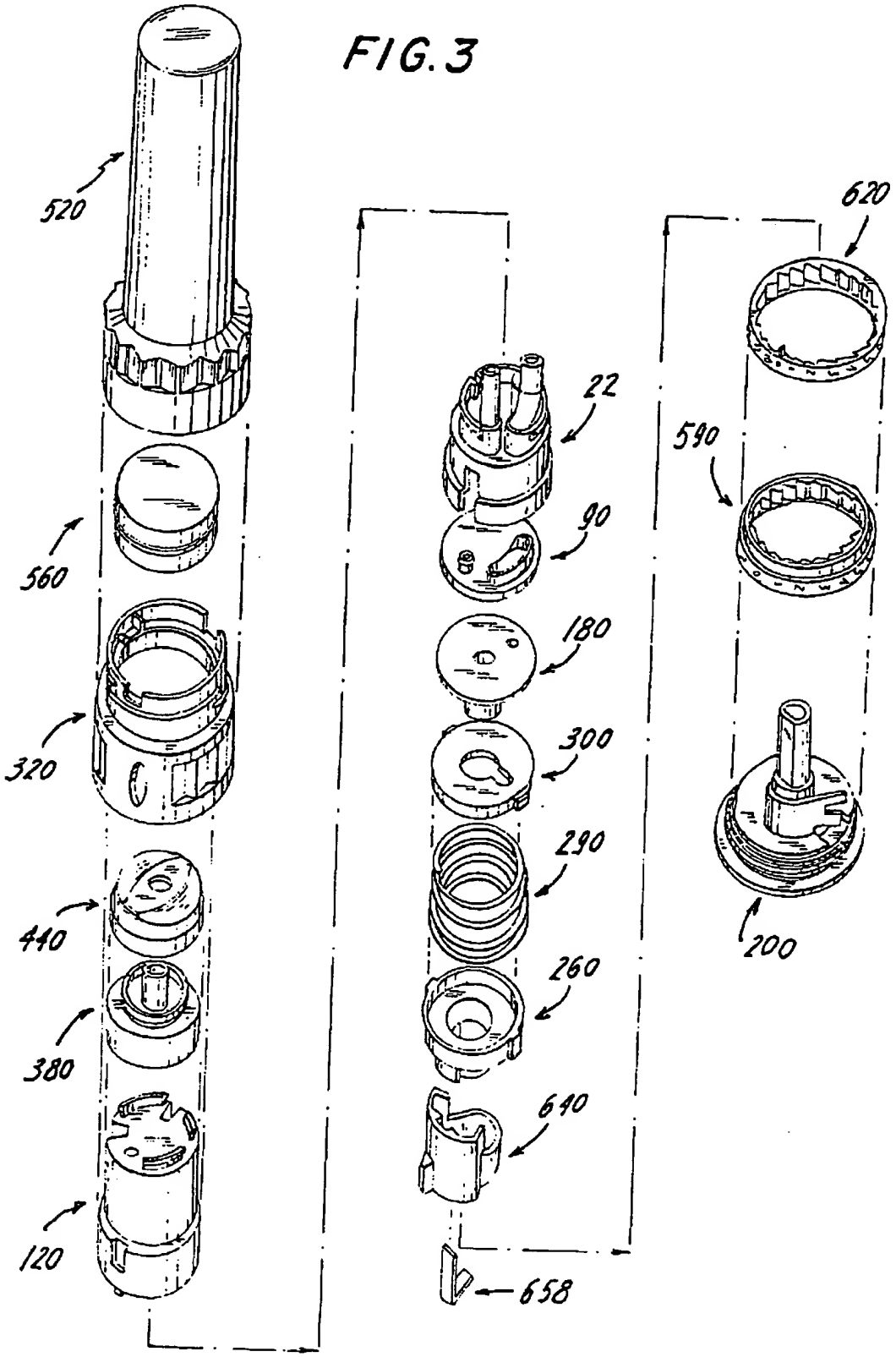


FIG. 4

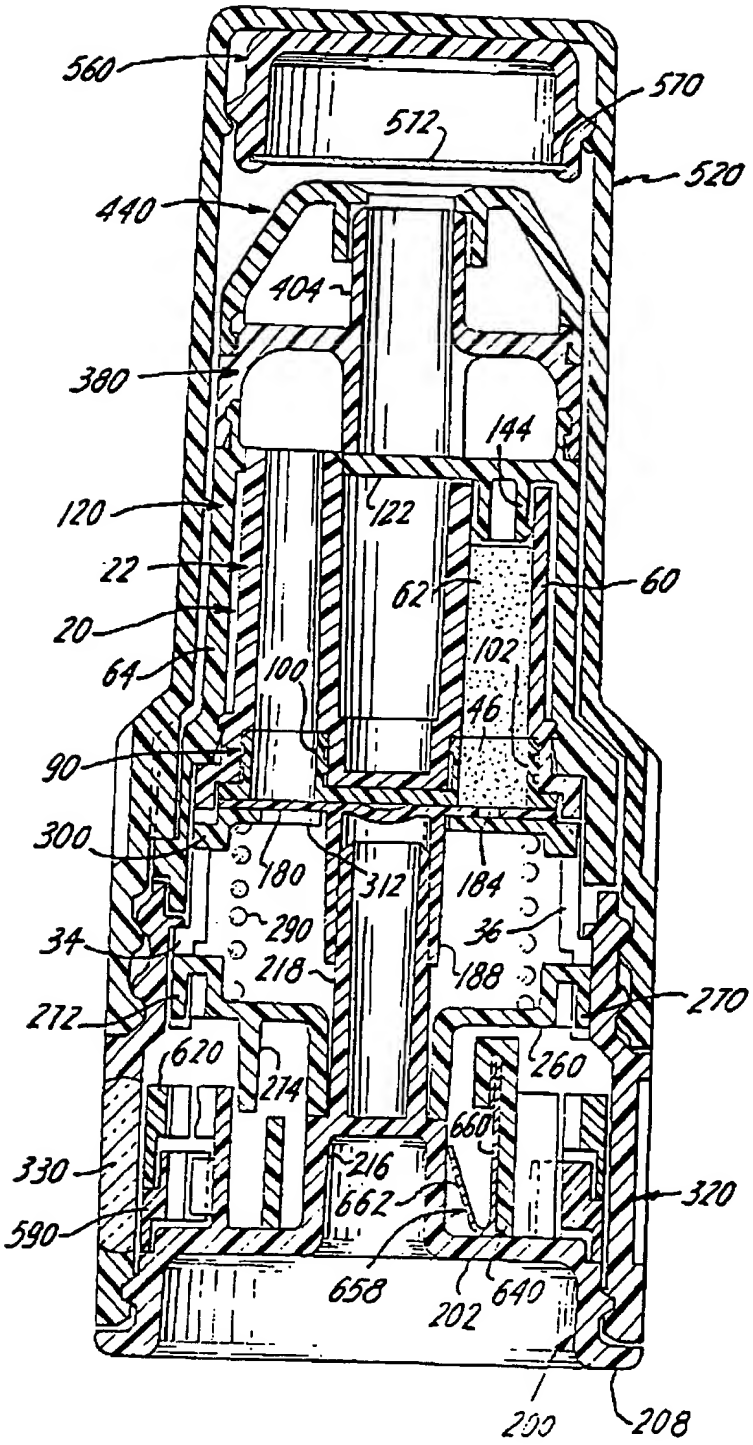

560
570
572
520
440
404
380
144
120
122
22
62
60
20
102
64
100
46
90
300
180
312
184
290
36
34
218
188
270
272
620
214
260
660
330
216
662
320
590
658
640
202
200
208

FIG. 5

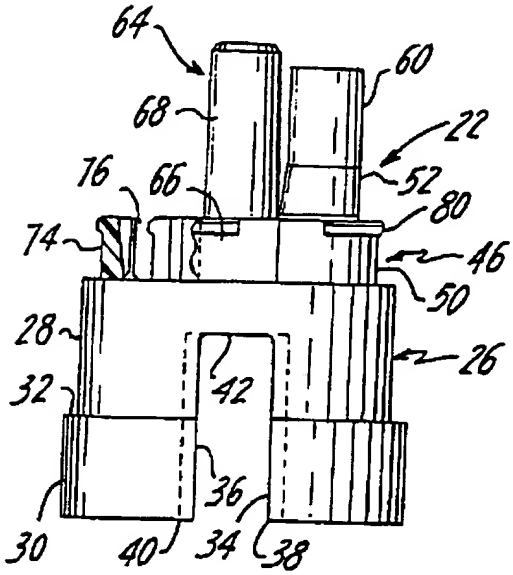
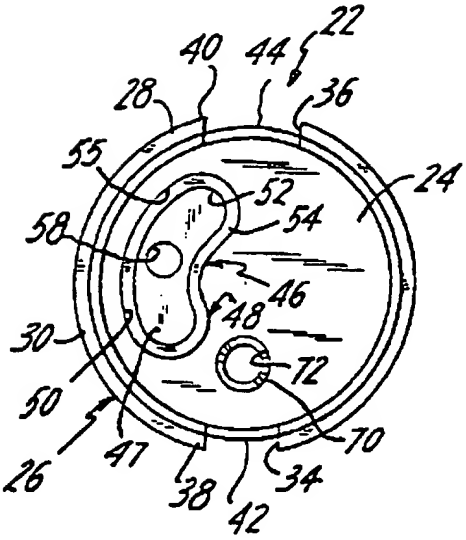


FIG. 7



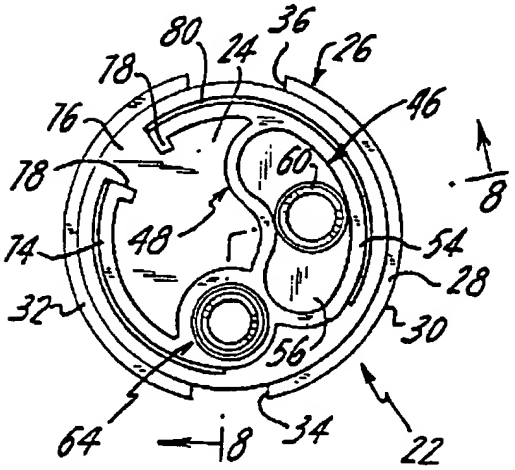


FIG. 6

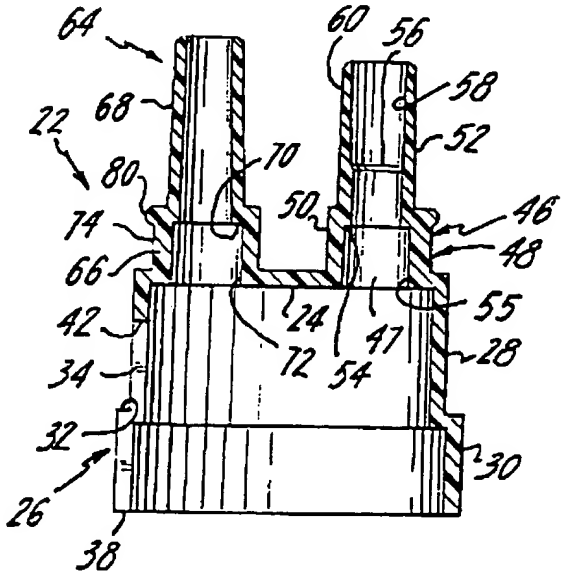


FIG. 8

FIG. 9

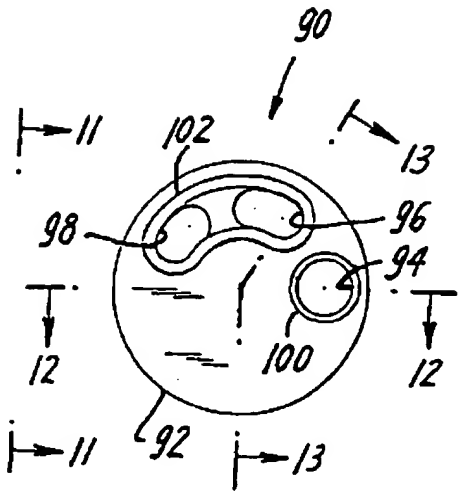


FIG. 11

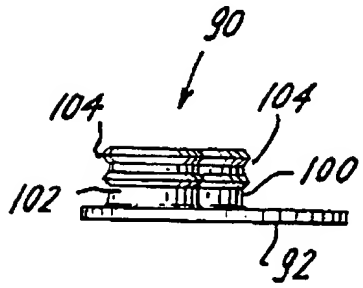


FIG. 12

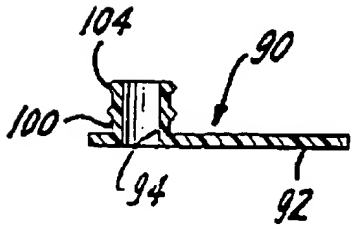


FIG. 10

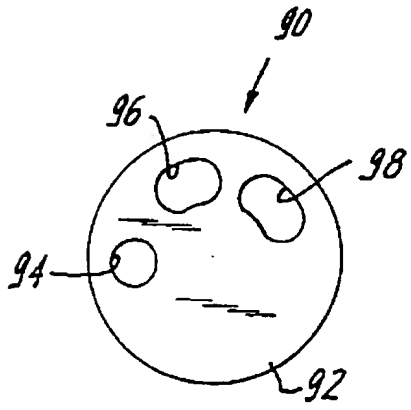


FIG. 13

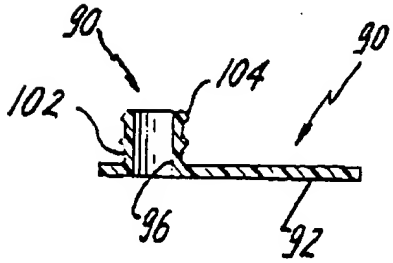


FIG.14

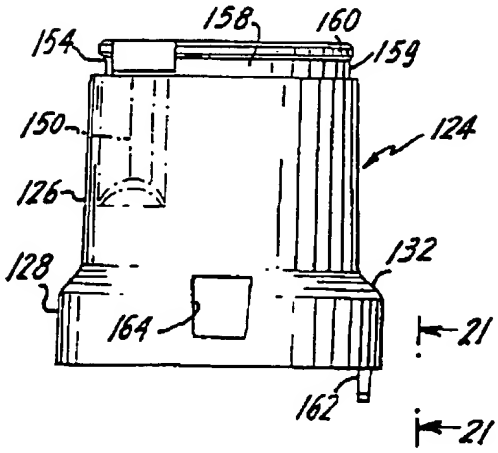


FIG.16

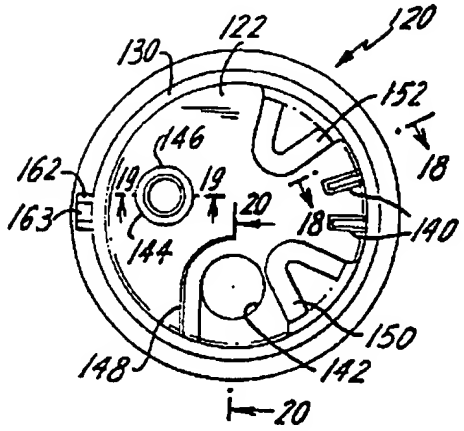
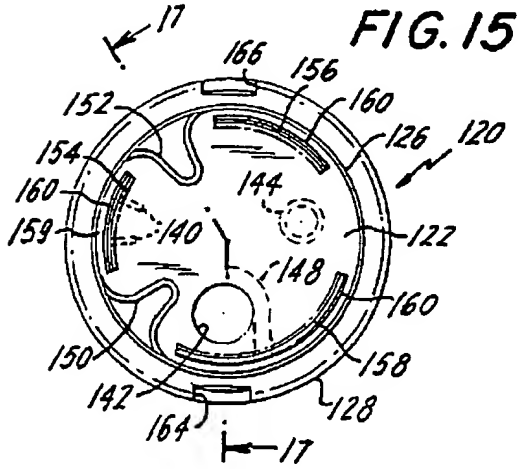


FIG.15



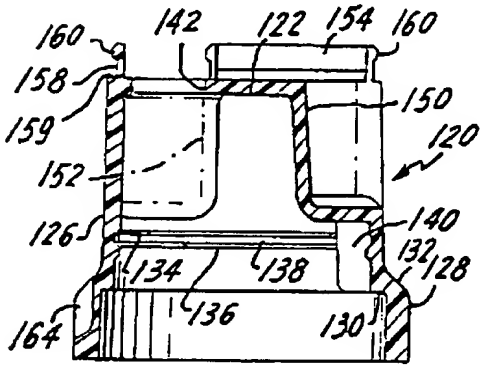


FIG.17

FIG.19

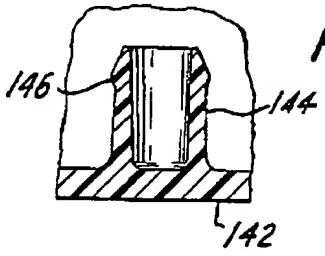


FIG.18

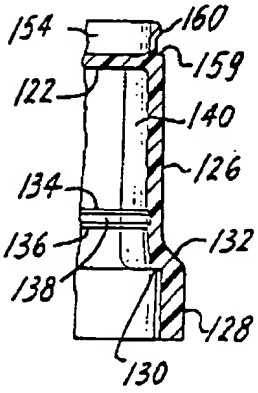


FIG.21

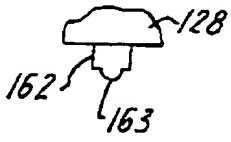


FIG.20

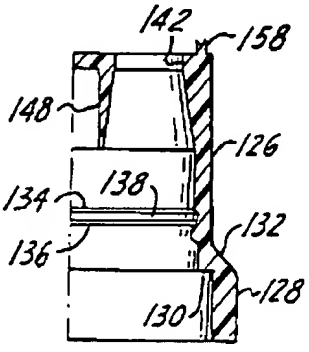


FIG.30

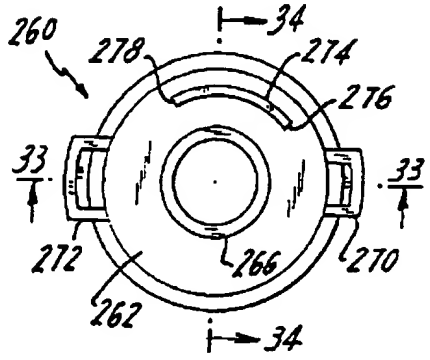


FIG.33

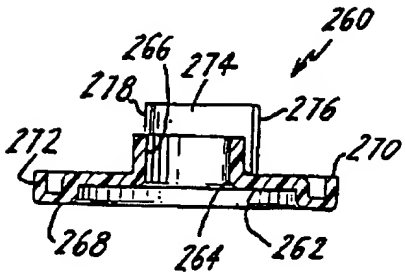


FIG.31

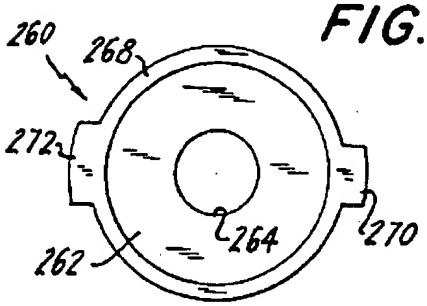


FIG.34

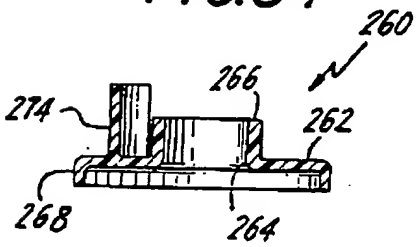


FIG.32

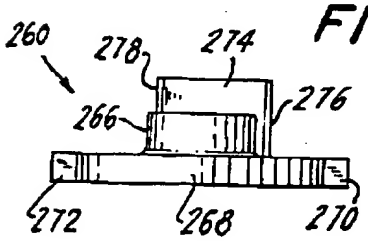


FIG.23

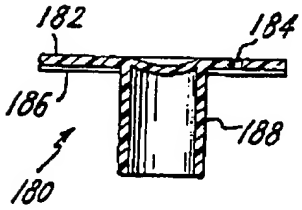


FIG.22

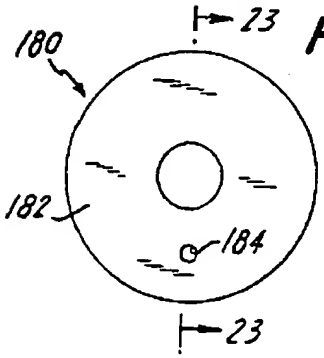


FIG.24

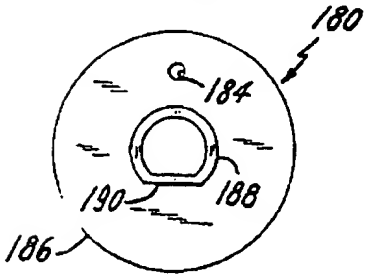


FIG. 25

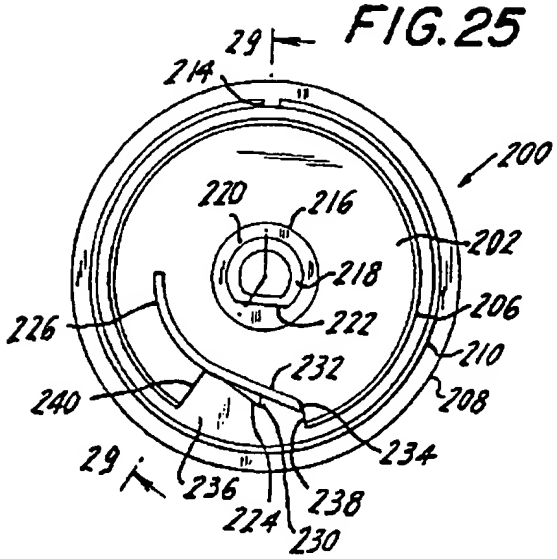


FIG. 26

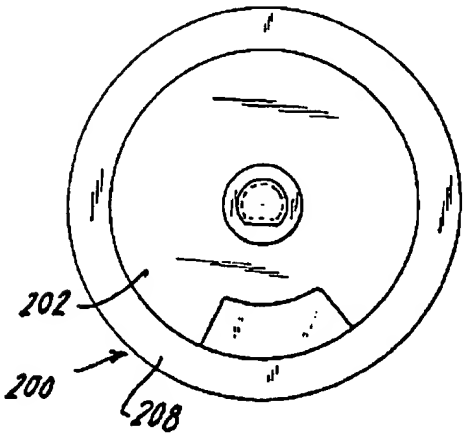


FIG. 27

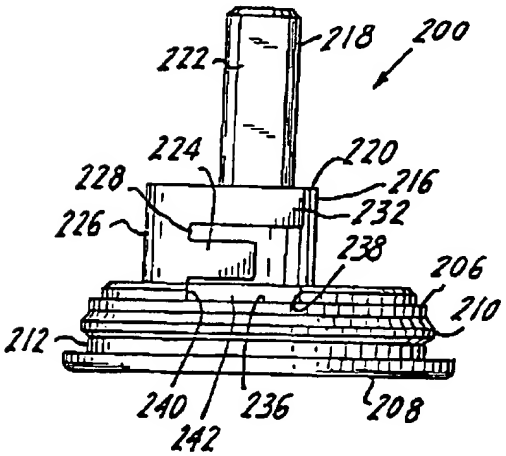


FIG. 28

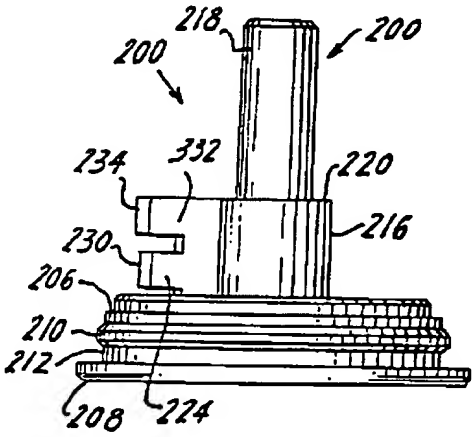
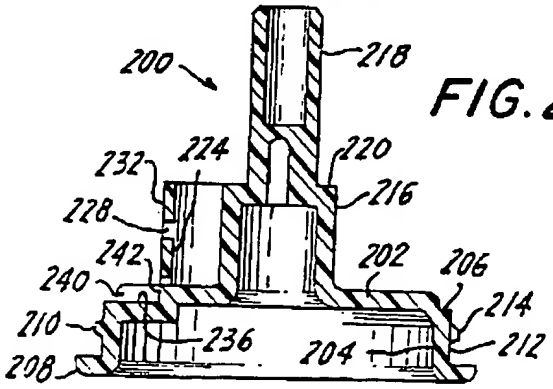


FIG. 29



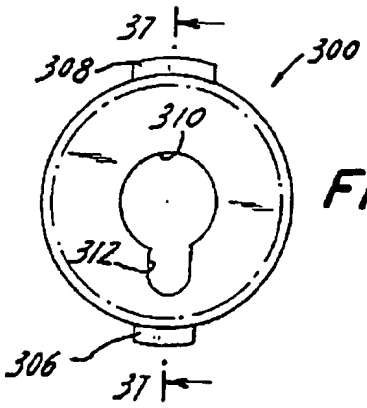


FIG.35

FIG.37

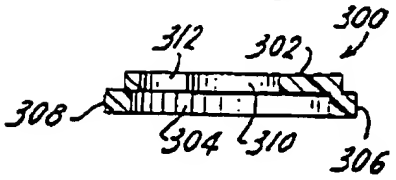


FIG.38

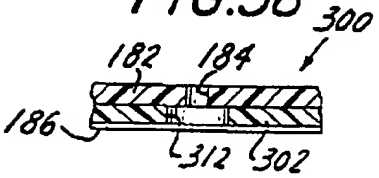


FIG.36

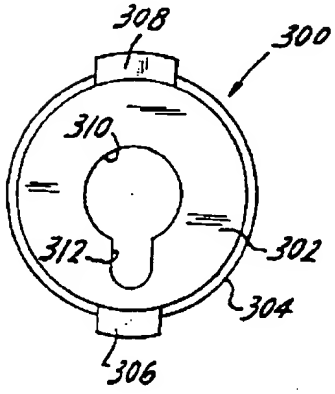


FIG.39

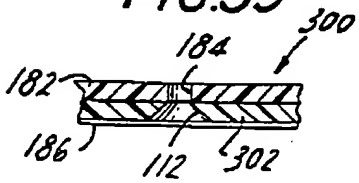


FIG.64

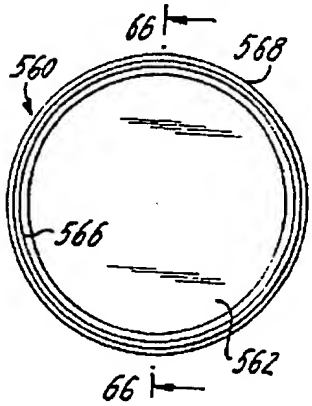


FIG.65

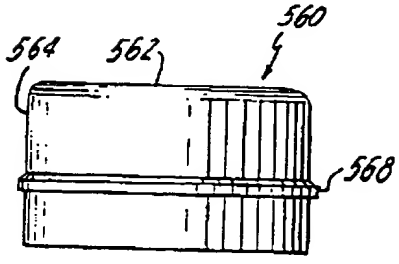


FIG.66

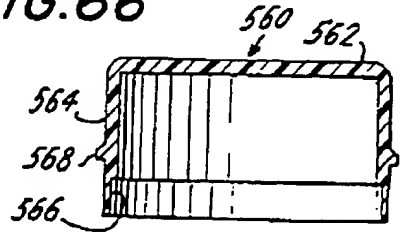


FIG. 40

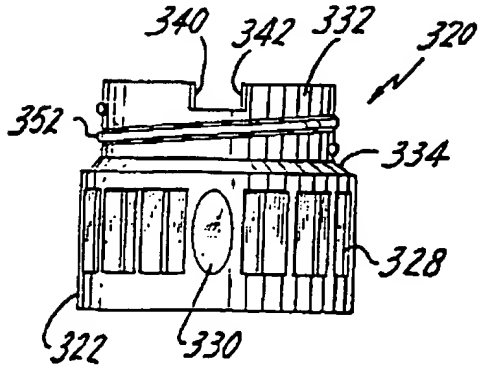


FIG. 41

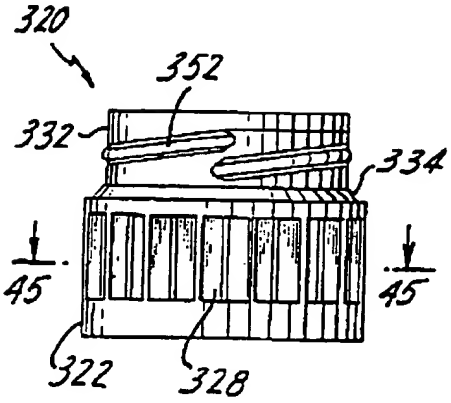


FIG. 42

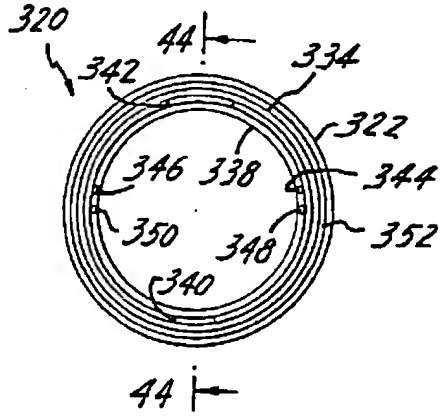


FIG. 43

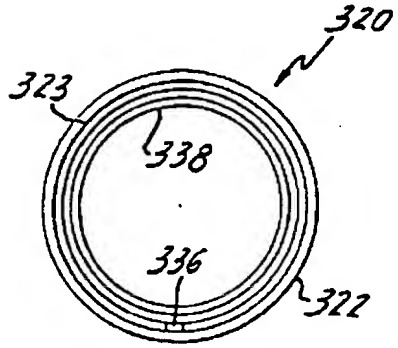


FIG. 44

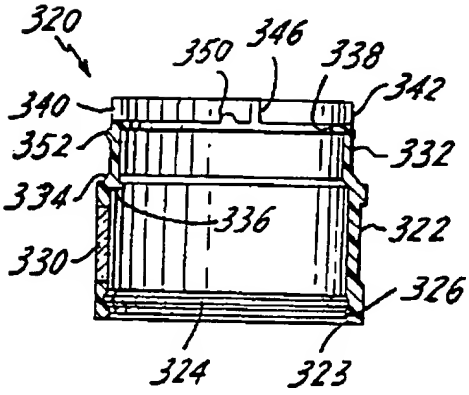


FIG. 45

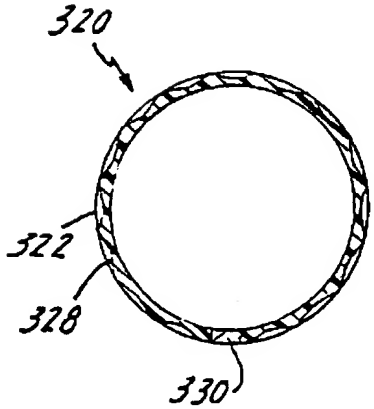


FIG. 46

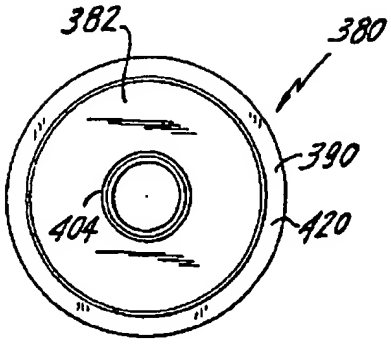


FIG. 47

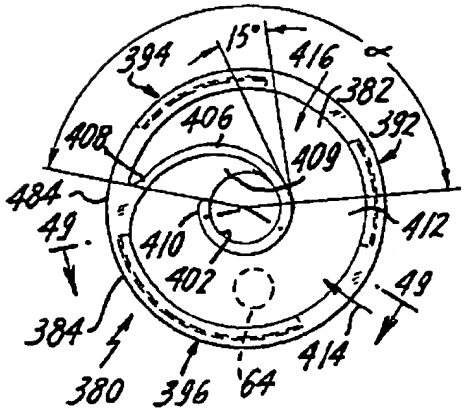


FIG. 48

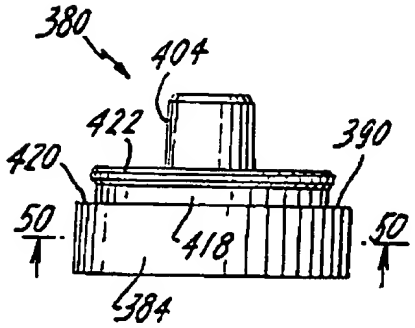


FIG. 49

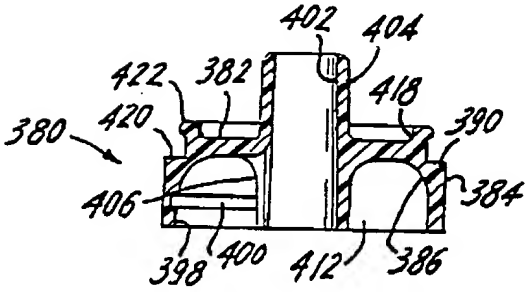


FIG. 50

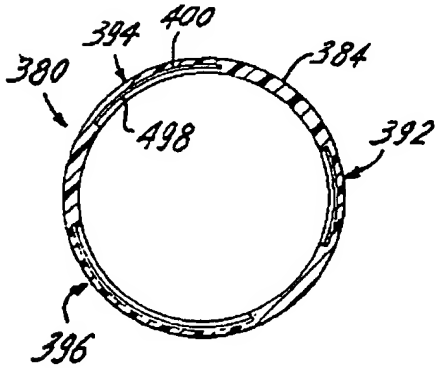


FIG.51

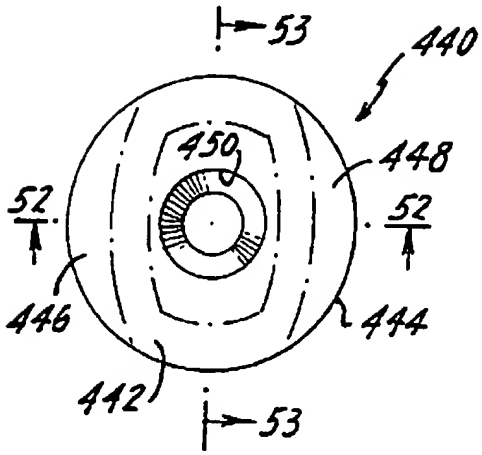


FIG.52

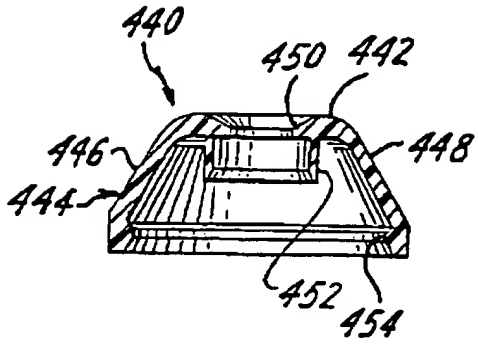


FIG.53

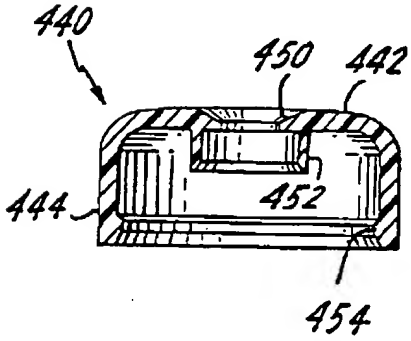


FIG.54

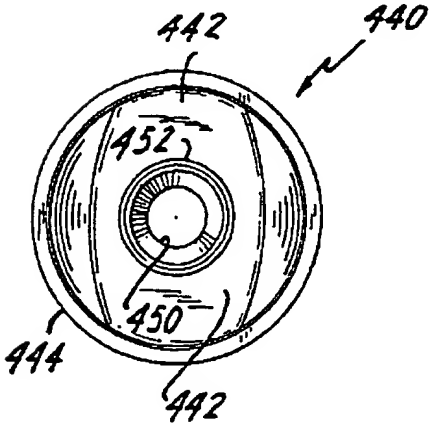


FIG.55

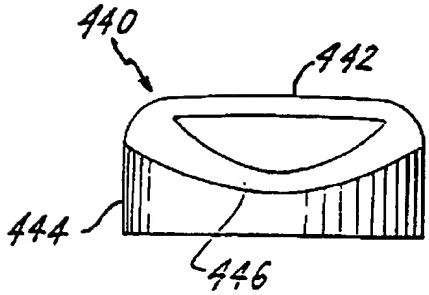


FIG. 56

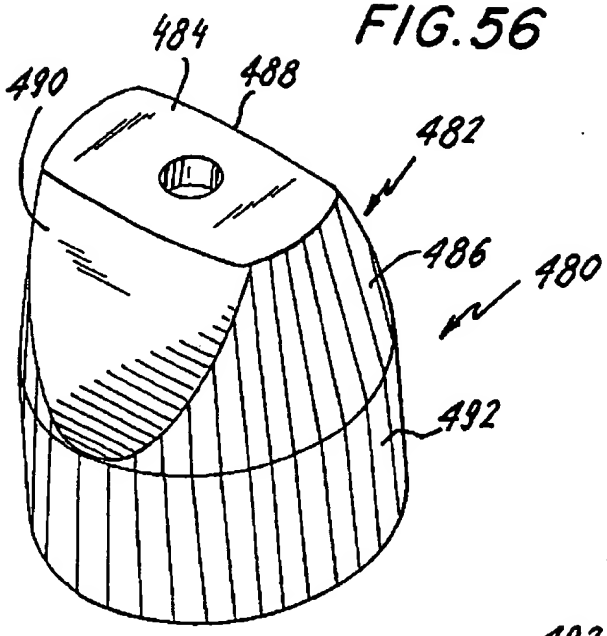
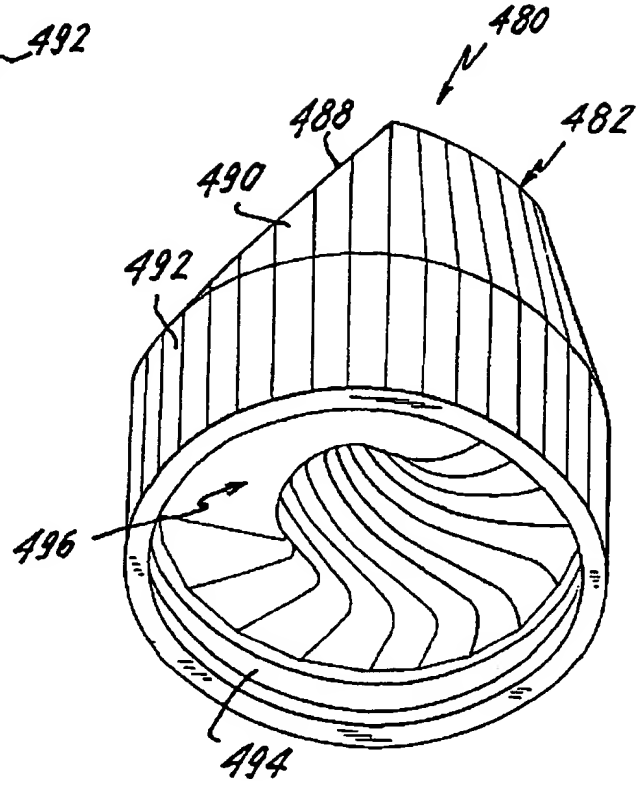


FIG. 57



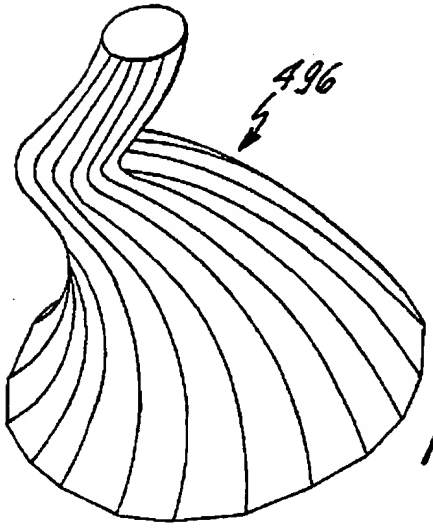


FIG. 58

FIG.59

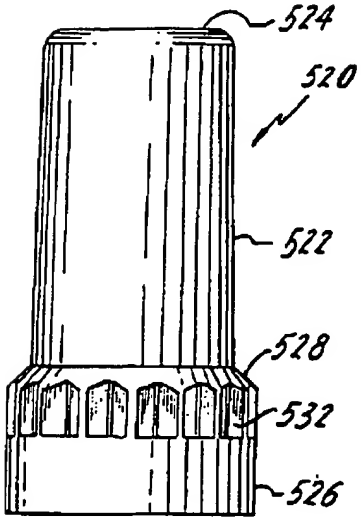
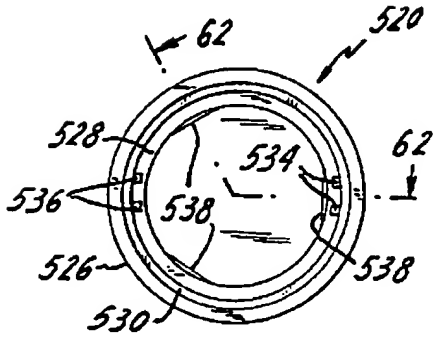


FIG.60



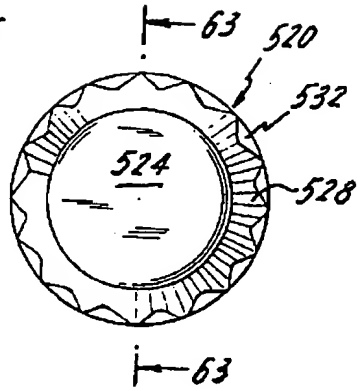


FIG.61

FIG.62

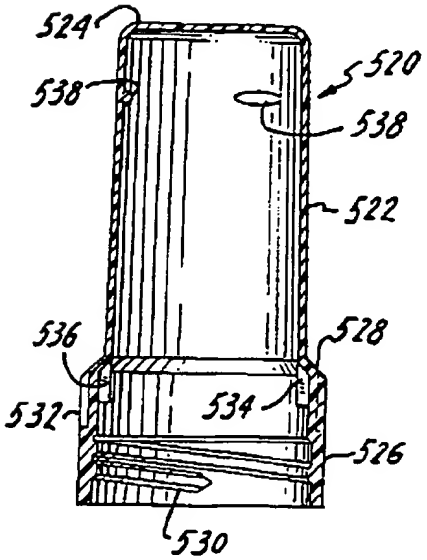


FIG.63

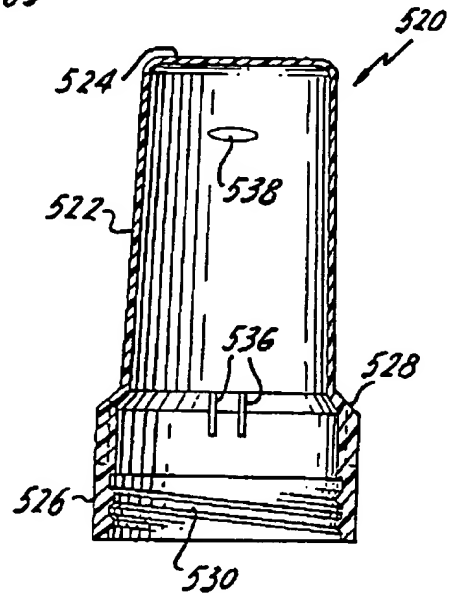


FIG. 67

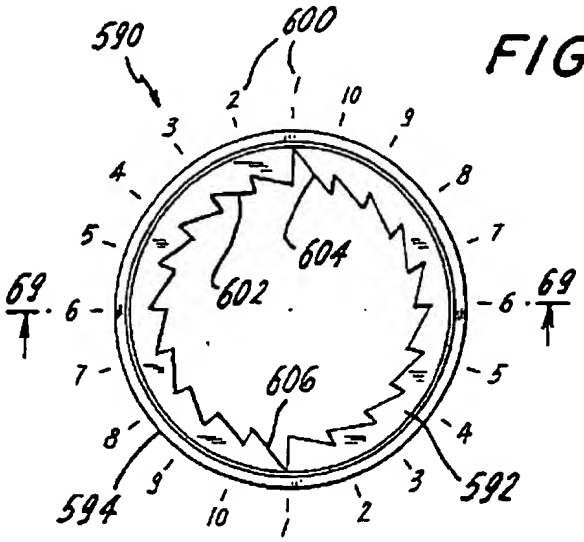


FIG. 69

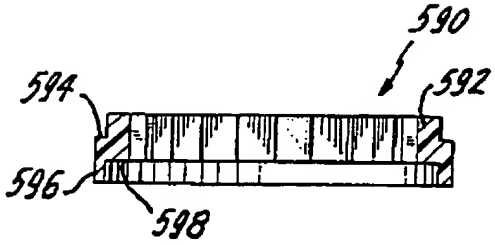


FIG. 68

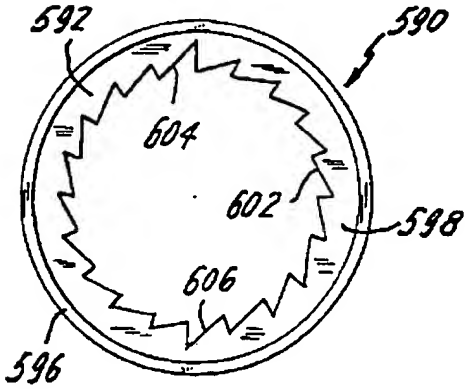


FIG. 70

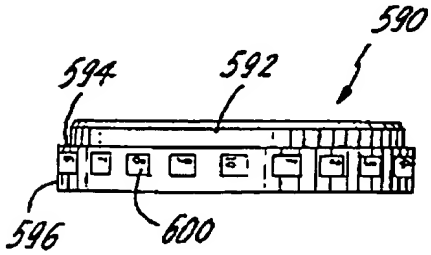


FIG. 71

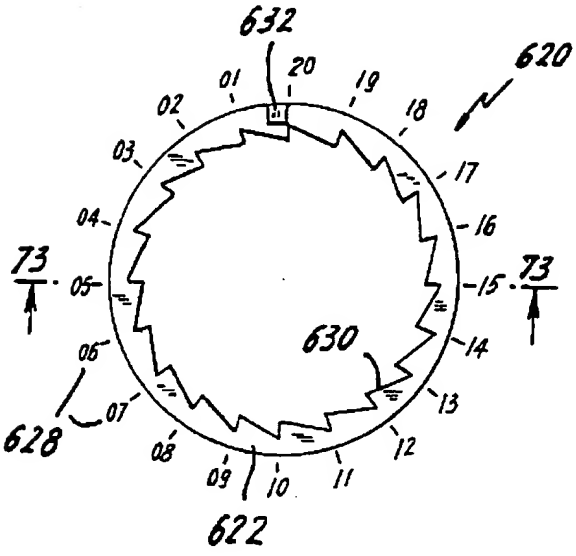


FIG. 73

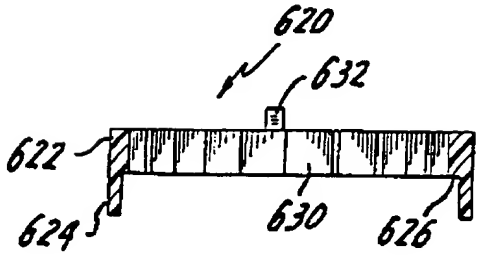


FIG. 72

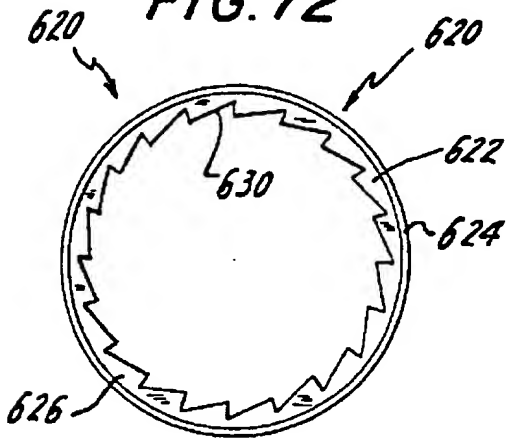


FIG. 74

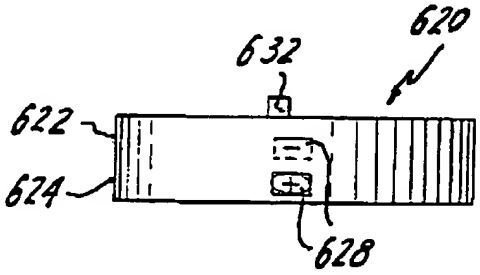


FIG. 75

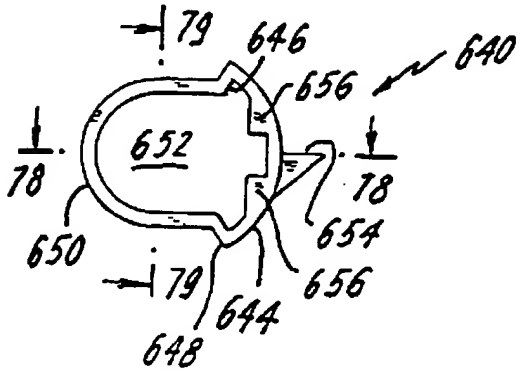
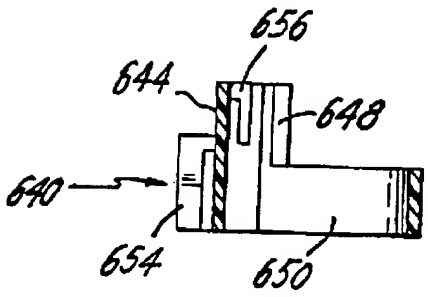


FIG. 78



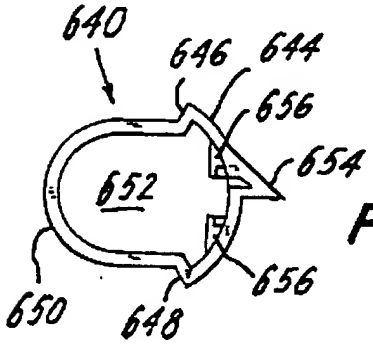


FIG. 76

FIG. 79

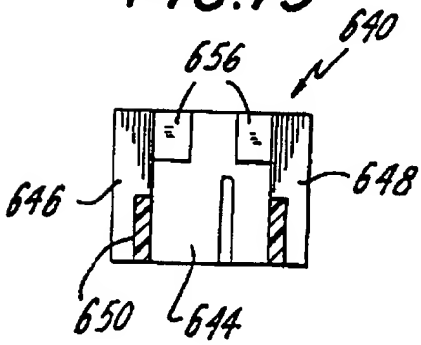


FIG. 77

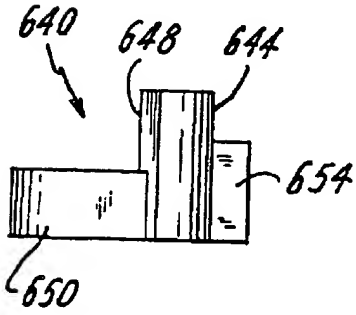


FIG.80

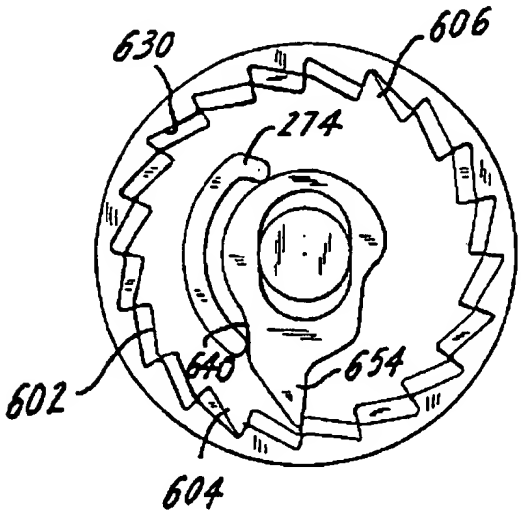
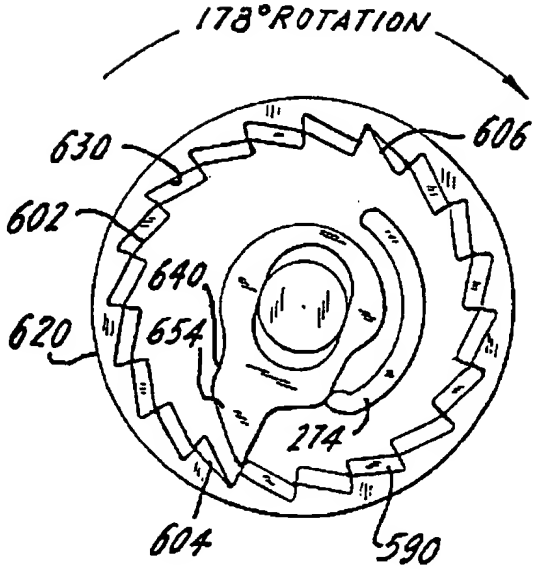


FIG.81



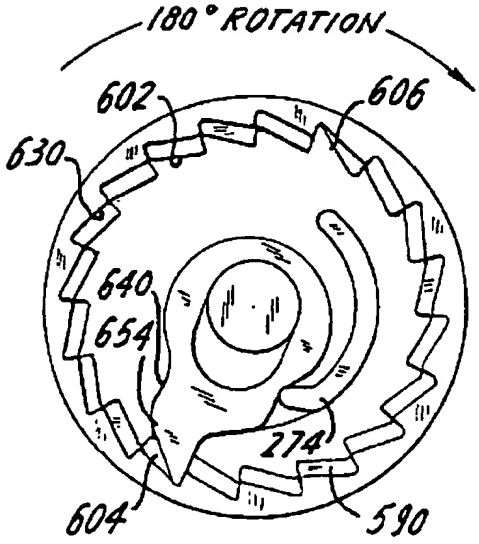


FIG.82

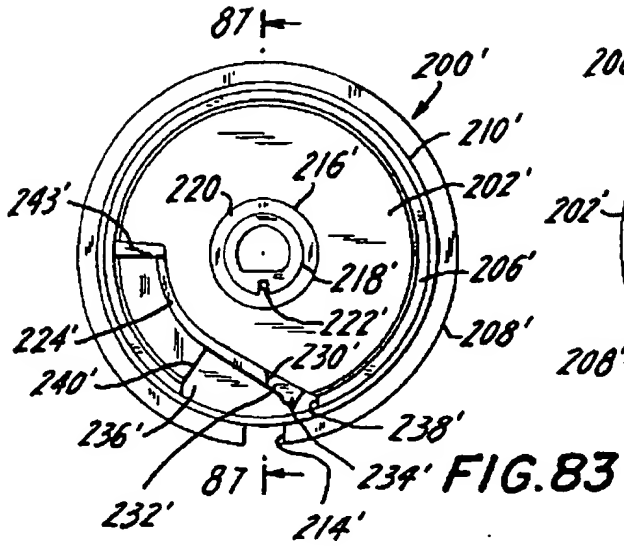


FIG.83

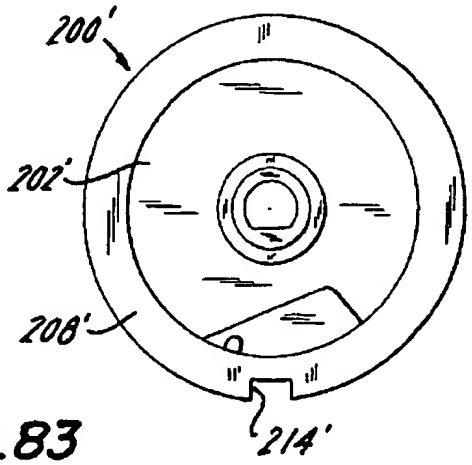


FIG.84

FIG.85

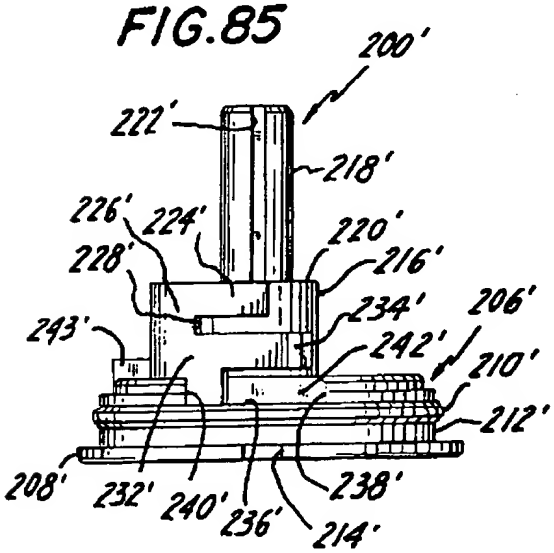
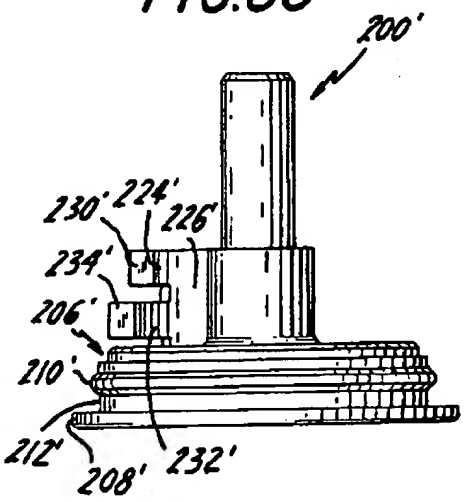


FIG.86



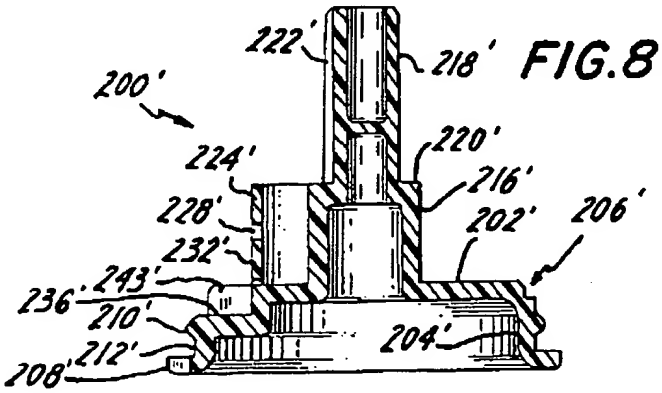


FIG.87

FIG.88

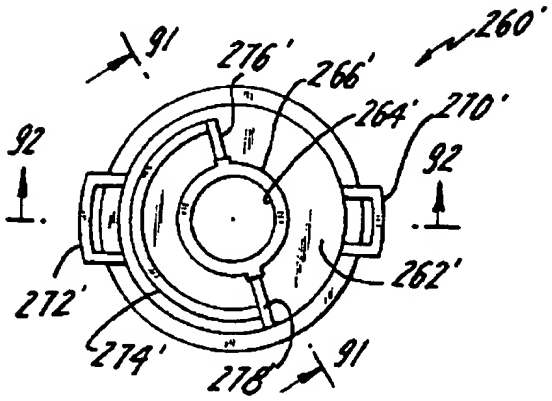


FIG.89

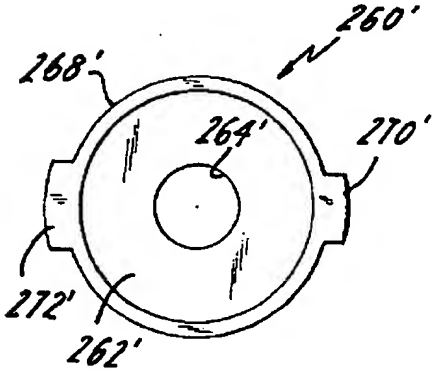


FIG.90

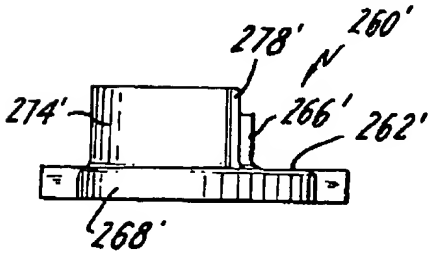
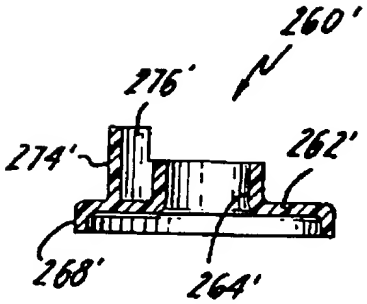


FIG.91



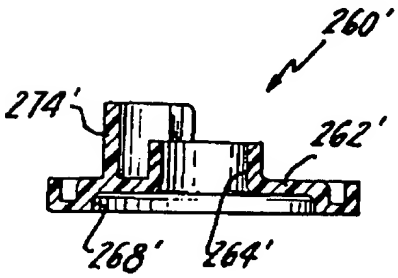


FIG.92

FIG.95

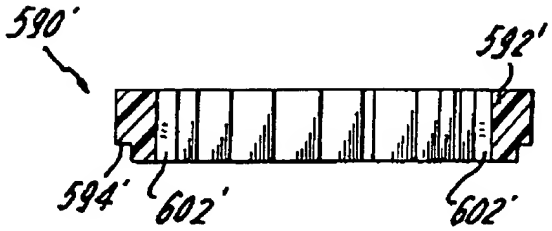


FIG.93

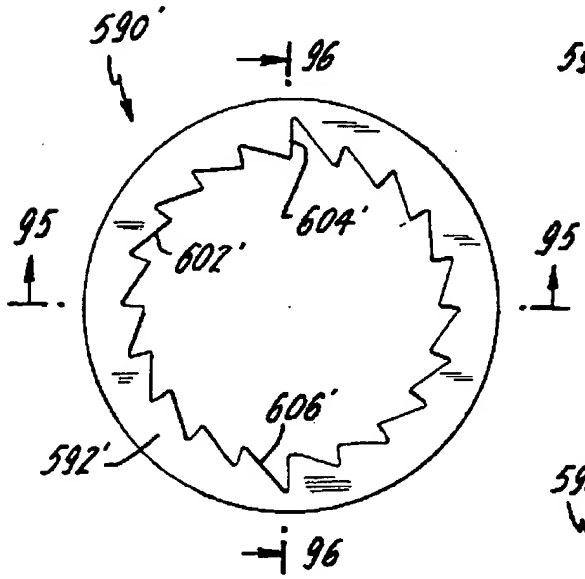
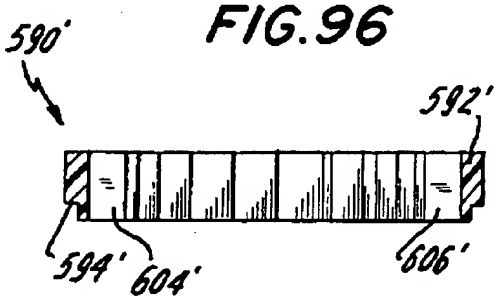


FIG.96



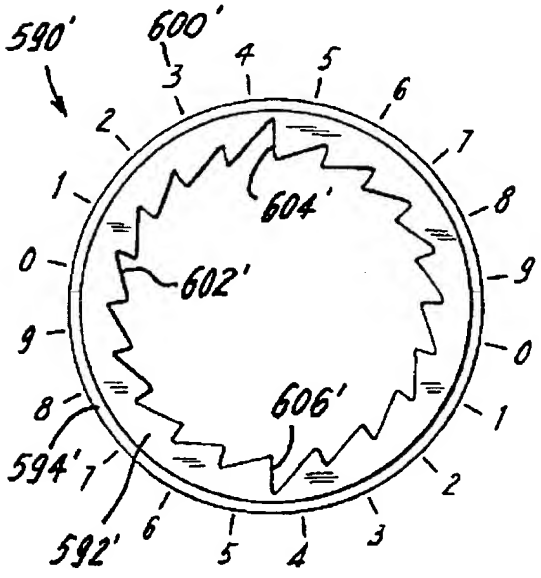


FIG.94

FIG.97

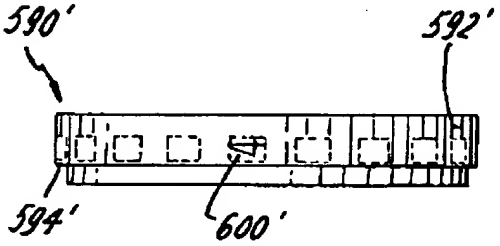


FIG.98

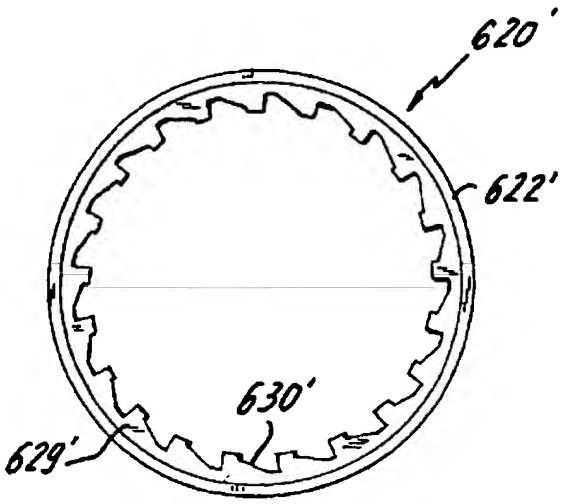


FIG.100

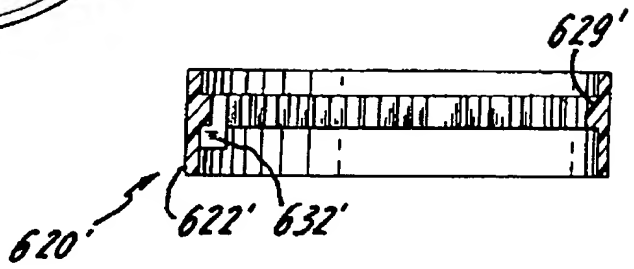


FIG.101

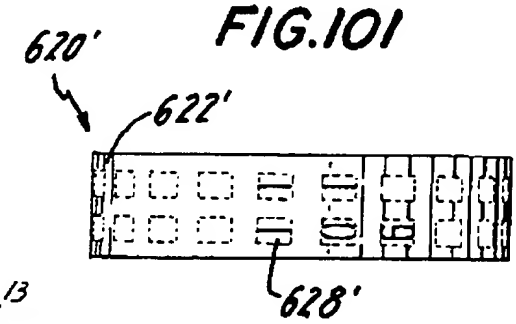
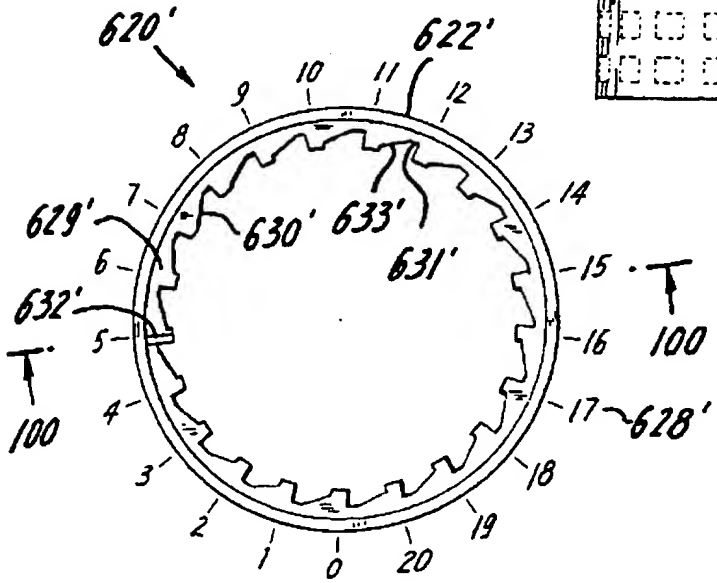


FIG.99



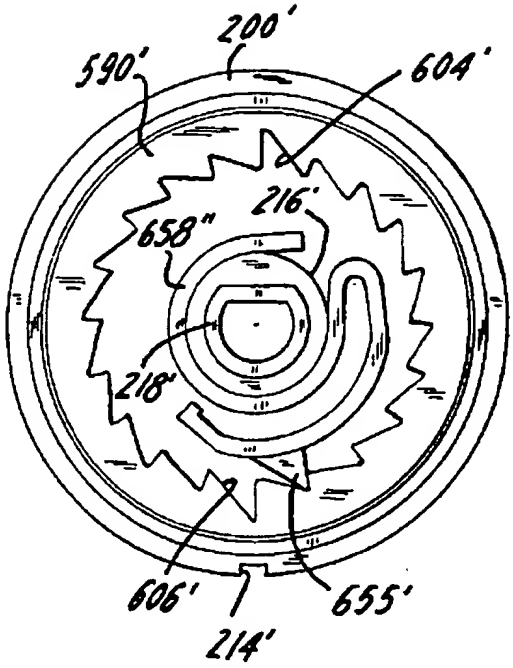
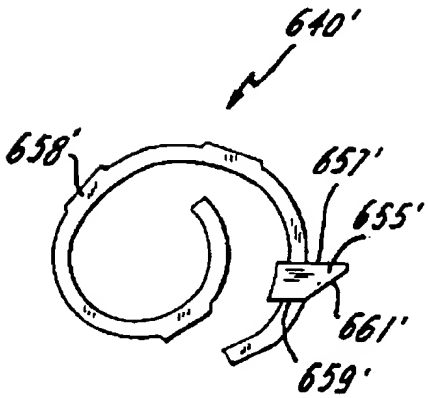


FIG.105

FIG.103



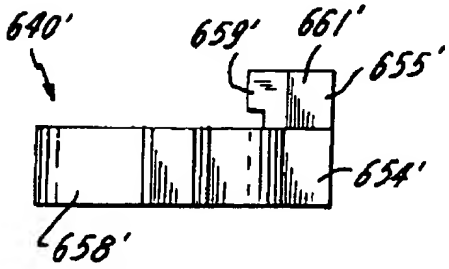
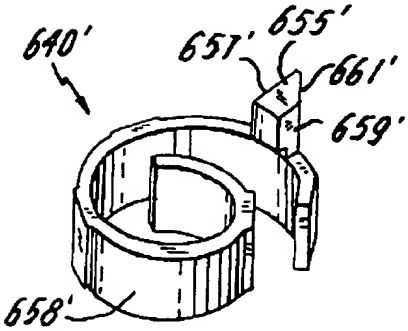


FIG.104

FIG.102



INHALER FOR POWDERED MEDICATIONS

INTRODUCTION TO THE INVENTION

This application is a 371 of PCT International application No. PCT/US93/12076, filed Dec. 16, 1993, which itself is a continuation-in-part of Ser. No. 08/992,959 filed Dec. 18, 1992, now abandoned.

The present invention relates generally to powder dispenser assemblies and, more particularly, is directed to a powder dispenser assembly used for inhalation of a metered dose of a powdered medicament.

When delivering medicaments, that is, pharmacologically active compounds, in solid form to the respiratory tract and to the lungs, careful attention to the accuracy of the dosage, which can be smaller than 0.1 milligram, must be made. This is because such medicaments are often quite potent, and the administration of excessive amounts thereof could be harmful to the patient. Further, if the dosage that is delivered is too small, it will not serve its purpose.

It is also necessary that the particles leaving the dispenser assembly be substantially within a particular size range, since particles of the medicament which are too large may not enter the respiratory tract, but instead, will be deposited in the mouth or pharynx and thence enter the digestive tract. As an example, preferred particles can have a diameter of 1 to 5 micrometers.

Various devices have been used in order to dispense a metered dose of powdered medicament, including pressurized aerosol devices, nebulizing devices, pump inhalators and the like. With the current concern over environmental issues, however, aerosol devices, which constitute a large part of the devices now on the market, are less favored. Further, with aerosol devices, the medicament is dissolved or suspended in a liquid propellant mixture, which results in the introduction of unneeded chemical substances into the body and further adds to the complexity of the devices.

In addition to the aforementioned types of dispenser assemblies, powder dispenser assemblies are also known. Studies have shown that there are virtually no significant differences in bronchodilator responses with equivalent amounts of medicinal substances administered either by powder dispensing devices or aerosol devices. Accordingly, there is now an ever-growing demand for powder dispensing devices which can dispense metered doses of powdered medicament. With such devices, the powder is automatically withdrawn during inspiration so there is less need to be concerned with synchronizing release of medication with the exact start of inspiration to insure quality of the product delivery.

U.S. Pat. No. 4,524,769 to Wetterlin, the entire disclosure of which is incorporated herein by reference, describes a dosing unit of the above type that includes a storage chamber for holding the active compound, a perforated membrane rotatably positioned under the storage chamber and a holder for the membrane. Introduction of the active compound into perforations in the perforated membrane is accomplished with elastic, spring-loaded scrapers, mounted in a holder in the storage chamber. With this arrangement, the membrane is movable between a first position where active compound is introduced by the scrapers in part of the area of the perforated membrane, and a second position where the part of the area of the loaded membrane has been inserted into the air conduit in the dosage inhalator. Thus, the active compound contained in the perforations is entrained at inhalation and brought through the nozzle to the respiratory tract and the lungs of the patient.

With this arrangement, a coil spring is used to bias the scrapers into engagement with the perforated membrane. The coil spring is interposed in the storage chamber between the casing and the scraper assembly. Alternatively, it is disclosed that the coil spring can be arranged so that the membrane is pressed against the scrapers, and thereby mounted in the base or maneuvering unit. In addition to the coil spring, Wetterlin uses spring loaded pins beneath the membrane to engage the ratcheted bottom of the membrane in order to provide distinct positions for the perforated membrane when it is advanced by the base or maneuvering unit. See also U.S. Pat. Nos. 4,907,583; 4,534,345; 4,667,668; and 4,805,811; all to Wetterlin.

U.S. Pat. No. 4,668,218 to Virtanen discloses a dispenser substantially identical to the Wetterlin patents, while also providing an indicating assembly which indicates the number of medicament dosages administered. However, Virtanen only provides a single counter ring, which consequently limits the counting capability of doses that are administered. In the case where a dispenser must dispense a large number of doses, for example 200 doses, the arrangement of Virtanen would be totally unacceptable. The limitation in Virtanen is due to the use of a single counter ring that is rotated about an axis orthogonal to the rotatably metering disc and which is rotated one increment for each horizontal rotation of the rotatable metering disc by means of a spiral ridge thereon.

Other disclosures of interest are in U.S. Pat. Nos. 3,085,745 to Auberger; 3,655,952 to Johnson et al; 4,565,302 to Pfeiffer et al; 4,817,822 to Rand et al; and 5,033,463 to Cocozza.

Further, in dry powder inhalers using micronized powder, there can be poor gravitational flow of the powder in micronized form. To improve handling qualities, the powder is processed into small agglomerate spheres having, for example, diameters of approximately one millimeter. During inhalation, the agglomerates are carried through the inhaler flow channels and must be broken up once again into micronized powder before the powder can be deposited in the patient's lungs. This is particularly so since the doses may be very small, on the order of 50 to 100 micrograms, and since particles larger than about 10 microns tend to lodge on surfaces of the mouth and pharynx. The agglomerates are typically much larger than 10 microns.

In known powder dispensers, in order to ensure that the powder is micronized and properly mixed with suction air, helical vanes have been included in the outlet conduit of the mouthpiece. See, for example, U.S. Pat. Nos. 4,907,583 to Wetterlin et al and 5,033,463 to Cocozza. However, such helical vanes do not adequately break up many powder agglomerates.

Still further, with the aforementioned powder dispensers, such as in U.S. Pat. No. 4,805,811 to Wetterlin, it is necessary to separately prime the device for each use, after the cover is removed. This becomes burdensome in practice.

SUMMARY OF THE INVENTION

In accordance with one aspect of the present invention, a counter for a powder dispenser includes a continuous counter ring having counting indicia thereon; an intermittent counter ring adjacent to the continuous counter ring, the intermittent counter ring having counting indicia thereon; display means through which one of the counting indicia from the continuous counter ring and one of the counting indicia from the intermittent counter ring are displayed to indicate a count corresponding to a number of doses of

powdered material that have been dispensed or remain to be dispensed; and actuating means for rotating the continuous counter ring one increment each time that a dose of the powdered material is dispensed to display another one of the counting indicia of the continuous counter ring, and for rotating the intermittent counter ring one increment for a predetermined number of rotational increments of the continuous counter ring to display another one of the counting indicia of the intermittent counter ring.

Specifically, the powder dispenser includes a base, and the continuous counter ring and the intermittent counter ring are rotatably mounted relative to the base. The continuous counter ring is rotatably mounted on the base, and the intermittent counter ring is rotatably mounted on the continuous counter ring coaxially with the continuous counter ring. The continuous counter ring has gear teeth therearound, the intermittent counter ring has gear teeth therearound, and the actuating means further includes pawl means, engaging with the gear teeth of the continuous counter ring and the intermittent counter ring, for rotating the continuous counter ring one increment each time that a dose of the powdered material is dispensed to display another one of the counting indicia of the continuous counter ring through the display means, and for rotating the intermittent counter ring one increment every predetermined number of rotational increments of the continuous counter ring to display another one of the counting indicia of the intermittent counter ring through the display means.

The gear teeth of the continuous counter ring are arranged in correspondence with the counting indicia thereon, and the gear teeth of the intermittent counter ring are arranged in correspondence with the counting indicia thereon, on inner surfaces of the respective rings. Further, spring means is provided for biasing the pawl means into engagement with the gear teeth of the continuous counter ring and the intermittent counter ring.

More particularly, the gear teeth of the continuous counter ring include a plurality of successive first gear teeth of a first depth and at least one second gear tooth of a second, greater depth, each the second gear tooth being positioned after every predetermined number of the first gear teeth; and the intermittent counter ring includes a plurality of successive third gear teeth of a depth equal to the depth of each the second gear tooth of the continuous counter ring so that the pawl means engages with successive ones of the first gear teeth during successive dosing operations and engages with one the second gear tooth of the continuous counter ring and one the third gear tooth of the intermittent counter ring after a plurality of the dosing operations.

In addition, detent means is provided for preventing rotation of the continuous counter ring and the intermittent counter ring in a second rotational direction opposite to the first rotational direction in which the pawl means drives the counter rings.

Pawl driver means is provided for incrementally rotating the pawl means, the pawl driver means including a retainer rotatably mounted on the base coaxially with the continuous counter ring and the intermittent counter ring, the retainer including first pawl driver means for engaging with one side of the pawl means to incrementally rotate the pawl means in a first rotational direction at the end of rotation of the retainer in the first rotational direction to cause the pawl means to engage a successive gear tooth of the continuous counter ring, and second pawl driver means for engaging an opposite side of the pawl means to incrementally rotate the pawl means in a second, opposite rotational direction at the end of rotation of the retainer in the second, opposite rotational direction to cause the pawl means to incrementally rotate the continuous counter ring therewith. The first and second pawl driver means are formed as opposite edges of an arcuate pawl driving wall connected with the retainer, wherein the first and second pawl driver means are spaced apart by a distance such that rotation of the retainer by a first arcuate distance causes incremental rotation of the pawl means by a second smaller arcuate distance. Preferably, the first arcuate distance is approximately 180° and the second arcuate distance is approximately 18°.

The above counter is provided in a powder dispenser including powder housing means for holding a supply of powdered material to be dispensed, the powder housing means including an inhalation conduit extending therethrough in displaced relation to the supply of powdered material; and metering plate means for holding a metered amount of the powdered material, the metering plate means including metered dose hole means for holding the metered amount of the powdered material, the metering plate means being positionable below the supply of powdered material, and the metering plate means and the powder housing means being relatively rotatable with respect to each other about a common central axis so that the metered dose hole means is adapted to be in fluid communication selectively with the supply of powdered material or the inhalation conduit. The powder dispenser includes a base having an axially extending retaining post thereon coaxial with the common axis, and the counter rings are rotatably mounted on the base in surrounding relation to the retaining post.

Further, the powder housing means includes holding means for carrying the retainer with the powder housing means during the relative rotation between the metering plate means and the powder housing means about the common central axis. The holding means includes at least one drive slot in the powder housing means and at least one driven ear in the retainer, the at least one drive ear engaging within the at least one drive slot.

In addition, spring means is provided for biasing the metering plate means and the powder housing means toward each other.

In accordance with another aspect of the present invention, a nozzle for breaking up agglomerates of powdered material from an inhalation conduit extending in a first direction in a powder dispenser to form micronized powdered material and for mixing the micronized powdered material with suction air, includes cavity means for changing the direction of flow of the powder from the first direction of the inhalation conduit to a second direction different from the first direction, and swirl means for substantially continuously changing the direction of flow of the powder in the second direction in the cavity means.

The cavity means is defined by a top wall and a skirt connected to a periphery of the top wall in surrounding relation to the swirl means. The top wall includes an opening for changing the direction of flow of the powder from the second direction of the cavity means substantially back to the first direction. Preferably, the top wall has a circular shape and the opening is centrally located in the top wall.

The swirl means includes a curved wall extending from the opening to the skirt, the curved wall extending in a substantially spiral manner. Specifically, the curved wall has a first curved wall section extending partially about the central opening and a second curved wall section extending from one end of the first curved wall section to the skirt, each of the first and second curved wall sections extending

essentially along a circular arc, with the radius of the circular arc of the second curved wall section being greater than the radius of the circular arc of the first curved wall section. The curved wall is connected with the top wall.

Chimney means extends from the top wall in surrounding relation to the central opening for changing the direction of flow of the powder from the second direction of the cavity means substantially back to the first direction. The chimney means has a central axis and the inhalation conduit has a central axis parallel to and offset from the central axis of the chimney means.

In accordance with still another aspect of the present invention, a nozzle for breaking up agglomerates of powdered material from an inhalation conduit extending in a first direction in a powder dispenser to form micronized powdered material and for mixing the micronized powdered material with suction air, the nozzle includes an outer wall defining a conduit with a shape substantially that of an inverted tornado.

Specifically, the inverted tornado shape is defined by a continuously changing cross-sectional circular area having a radius which changes exponentially by depth from a lower outer circle of a first radius to an upper circle of a second, smaller radius, and having an origin which moves in a circle that changes with depth. More particularly, the inverted tornado shape is defined by the equation:

$$(x-a)^2+(y-b)^2=c_0+c_1*e^{-kz},$$

where

$a=a_0*\sin(a_1*\pi)$,

$b=b_0*\cos(b_1*\pi)$,

c_0+c_1 is the radius of a lowest cross-sectional circular area of the inverted tornado shape,

c_0 is the radius of an uppermost cross-sectional circular area of the inverted tornado shape,

a_0+a_1 is the x-coordinate of the lowest cross-sectional circular area,

a_0 is the x-coordinate of the uppermost cross-sectional circular area,

b_0+b_1 is the y-coordinate of the lowest cross-sectional circular area,

b_0 is the x-coordinate of the uppermost cross-sectional circular area,

x, y and z are x-, y- and z- coordinates, and

k is an exponential coefficient which defines the geometry of a spiral of the inverted tornado shape.

In accordance with yet another aspect of the present invention, a gas permeable retainer means is provided for retaining a dose of the powdered material in the metered dose hole means, the retainer means being positioned below the metered dose hole means. In one embodiment, the retainer means includes a material secured to an underside of the metering plate means and formed by a material selected from the group consisting of a gas-permeable filter, a mesh screen, a porous material and a perforated plate element.

The powder dispenser includes an upper support plate positioned below and in contact with the metering plate means, the upper support plate having an opening larger than the metered dose hole means and in alignment with the metered dose hole means when the metered dose hole means is in alignment with the inhalation conduit, and in an alternative embodiment, the retainer means includes a material secured to an underside of the upper support plate and formed by a material selected from the group consisting of a gas-permeable filter, a mesh screen, a porous material and a perforated plate element.

In addition, rotation limiting means is provided for limiting bi-directional relative rotation between the powder housing means and the metering disc means to a predetermined angle of rotation, for example, 180°.

Lock-out means is also provided for preventing the relative rotation of the powder housing means and the metering plate means after a predetermined number of doses have been dispensed. In this regard, the powder dispenser includes a base on which the metering plate means is non-rotatably mounted and an adapter is non-rotatably mounted on the base. The lock-out means includes a dosage limiter tab on the adapter, and tab means on the counter means for engaging with the dosage limiter tab when the predetermined number of doses have been dispensed.

In accordance with a further aspect of the present invention, the powder dispenser includes closure cap means for covering the powder housing means and for priming the powder dispenser for use, the closure cap means including priming means for rotating the powder housing means such that the inhalation conduit is in communication with the metered dose hole means when the closure cap means is removed from covering relation of the powder housing means, and for rotating the powder housing means such that the inhalation conduit is out of communication with the metered dose hole means and such that the powder supply opening comes into communication with the metered dose hole means as the closure cap means is secured in covering relation to the powder housing means.

Specifically, the adapter includes first helical threads and the closure cap means includes second helical threads for engaging with the first helical threads to threadedly connect the closure cap means on the adapter. The powder housing means includes at least one driving recess and the priming means includes rib means on an inside surface of the closure cap means for engaging with the at least one driving recess to rotate the powder housing means such that the inhalation conduit is in communication with the metered dose hole means when the closure cap means is threadedly removed from the covering relation of the powder housing means and for rotating the powder housing means such that the inhalation conduit is out of communication with the metered dose hole means and such that the powder supply opening comes into communication with the metered dose hole means as the closure cap means is threadedly secured to the adapter means in covering relation to the powder housing means.

The above and other features of the invention will become readily apparent from the following detailed description thereof which is to be read in connection with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of a metered powder dose dispenser according to the present invention;

FIG. 2 is a perspective view of the metered powder dose dispenser of FIG. 1, with the closure cap removed;

FIG. 3 is an exploded perspective view of the metered powder dose dispenser of FIG. 1;

FIG. 4 is a longitudinal cross-sectional view of the metered powder dose dispenser of FIG. 1;

FIG. 5 is a front elevational view, partially in cross-section, of the reservoir body of the metered powder dose dispenser of FIG. 1;

FIG. 6 is a top plan view of the reservoir body of FIG. 5;

FIG. 7 is a bottom plan view of the reservoir body of FIG. 5;

FIG. 8 is a cross-sectional view of the reservoir body of FIG. 6, taken along line 8—8 thereof;

FIG. 9 is a top plan view of the reservoir plug of the metered powder dose dispenser of FIG. 1;

FIG. 10 is a bottom plan view of the reservoir plug of FIG. 9;

FIG. 11 is a side elevational view of the reservoir plug of FIG. 9, viewed from line 11—11 thereof;

FIG. 12 is a cross-sectional view of the reservoir plug of FIG. 9, taken along line 12—12 thereof;

FIG. 13 is a cross-sectional view of the reservoir plug of FIG. 9, taken along line 13—13 thereof;

FIG. 14 is a front elevational view of the driving body of the metered powder dose dispenser of FIG. 1;

FIG. 15 is a top plan view of the driving body of FIG. 14;

FIG. 16 is a bottom plan view of the driving body of FIG. 14;

FIG. 17 is a cross-sectional view of the driving body of FIG. 15, taken along line 17—17 thereof;

FIG. 18 is a cross-sectional view of the driving body of FIG. 16, taken along line 18—18 thereof;

FIG. 19 is a cross-sectional view of the driving body of FIG. 16, in inverted position, taken along line 19—19 thereof;

FIG. 20 is a cross-sectional view of the driving body of FIG. 16, taken along line 20—20 thereof;

FIG. 21 is a side elevational view showing the counter stop tab of the driving body of FIG. 14, viewed along line 21—21 thereof;

FIG. 22 is a top plan view of the metering dose plate of the metered powder dose dispenser of FIG. 1;

FIG. 23 is a cross-sectional view of the metering dose plate of FIG. 22, taken along line 23—23 thereof;

FIG. 24 is a bottom plan view of the metering dose plate of FIG. 22;

FIG. 25 is a top plan view of the base of the metered powder dose dispenser of FIG. 1;

FIG. 26 is a bottom plan view of the base of FIG. 25;

FIG. 27 is a front elevational view of the base of FIG. 25;

FIG. 28 is a side elevational view of the base of FIG. 25;

FIG. 29 is a cross-sectional view of the base of FIG. 25, taken along line 29—29 thereof;

FIG. 30 is a bottom plan view of the lower spring retainer of the metered powder dose dispenser of FIG. 1;

FIG. 31 is a top plan view of the lower spring retainer of FIG. 30;

FIG. 32 is a side elevational view of the lower spring retainer of FIG. 30;

FIG. 33 is a cross-sectional view of the lower spring retainer of FIG. 30, taken along line 33—33 thereof;

FIG. 34 is a cross-sectional view of the lower spring retainer of FIG. 30, taken along line 34—34 thereof;

FIG. 35 is a top plan view of the support plate of the metered powder dose dispenser of FIG. 1;

FIG. 36 is a bottom plan view of the support plate of FIG. 35;

FIG. 37 is a cross-sectional view of the support plate of FIG. 35, taken along line 37—37 thereof;

FIG. 38 is a cross-sectional view of a portion of the metering dose plate, support plate and powder retainer according to an alternative embodiment of the present invention;

FIG. 39 is a cross-sectional view of a portion of the metering dose plate, support plate and powder retainer according to another alternative embodiment of the present invention;

FIG. 40 is a front elevational view of the adapter of the metered powder dose dispenser of FIG. 1;

FIG. 41 is a side elevational view of the adapter of FIG. 40;

FIG. 42 is a top plan view of the adapter of FIG. 40;

FIG. 43 is a bottom plan view of the adapter of FIG. 40;

FIG. 44 is a cross-sectional view of the adapter of FIG. 42, taken along line 44—44 thereof;

FIG. 45 is a cross-sectional view of the adapter of FIG. 41, taken along line 45—45 thereof;

FIG. 46 is a top plan view of the swirl nozzle of the metered powder dose dispenser of FIG. 1;

FIG. 47 is a bottom plan view of the swirl nozzle of FIG. 46;

FIG. 48 is a side elevational view of the swirl nozzle of FIG. 46;

FIG. 49 is a cross-sectional view of the swirl nozzle of FIG. 47, taken along line 49—49 thereof;

FIG. 50 is a cross-sectional view of only the annular side wall of the swirl nozzle of FIG. 48, taken along line 50—50 thereof;

FIG. 51 is a top plan view of the mouthpiece of the metered powder dose dispenser of FIG. 1;

FIG. 52 is a cross-sectional view of the mouthpiece of FIG. 51, taken along line 52—52 thereof;

FIG. 53 is a cross-sectional view of the mouthpiece of FIG. 51, taken along line 53—53 thereof;

FIG. 54 is a bottom plan view of the mouthpiece of FIG. 51;

FIG. 55 is a side elevational view of the mouthpiece of FIG. 51;

FIG. 56 is a top perspective view of a combination mouthpiece nozzle according to another embodiment of the present invention;

FIG. 57 is a bottom perspective view of the mouthpiece nozzle of FIG. 56;

FIG. 58 is a perspective view of the shape of the internal swirl cavity of the mouthpiece nozzle of FIG. 56;

FIG. 59 is a side elevational view of the closure cap of the metered powder dose dispenser of FIG. 1;

FIG. 60 is a bottom plan view of the closure cap of FIG. 59;

FIG. 61 is a top plan view of the closure cap of FIG. 59;

FIG. 62 is a cross-sectional view of the closure cap of FIG. 60, taken along line 62—62 thereof;

FIG. 63 is a cross-sectional view of the closure cap of FIG. 61, taken along line 63—63 thereof;

FIG. 64 is a bottom plan view of a desiccant holder of the metered powder dose dispenser of FIG. 1;

FIG. 65 is a side elevational view of the desiccant holder of FIG. 64;

FIG. 66 is a cross-sectional view of the desiccant holder of FIG. 64, taken along line 66—66 thereof;

FIG. 67 is a top plan view of the continuous counter ring of the metered powder dose dispenser of FIG. 1;

FIG. 68 is a bottom plan view of the continuous counter ring of FIG. 67;

FIG. 69 is a cross-sectional view of the continuous counter ring of FIG. 67, taken along line 69—69 thereof;

FIG. 70 is a side elevational view of the continuous counter ring of FIG. 67;

FIG. 71 is a top plan view of the intermittent counter ring of the metered powder dose dispenser of FIG. 1;

FIG. 72 is a bottom plan view of the intermittent counter ring of FIG. 71;

FIG. 73 is a cross-sectional view of the intermittent counter ring of FIG. 71, taken along line 73—73 thereof;

FIG. 74 is a side elevational view of the intermittent counter ring of FIG. 71;

FIG. 75 is a top plan view of the pawl assembly of the metered powder dose dispenser of FIG. 1;

FIG. 76 is a bottom plan view of the pawl assembly of FIG. 75;

FIG. 77 is a side elevational view of the pawl assembly of FIG. 75;

FIG. 78 is a cross-sectional view of the pawl assembly of FIG. 75, taken along line 78—78 thereof;

FIG. 79 is a cross-sectional view of the pawl assembly of FIG. 75, taken along line 79—79 thereof;

FIG. 80 is a schematic view showing the relationship between the arcuate pawl driving wall of the lower spring retainer, the continuous counter ring, the intermittent counter ring and the pawl assembly in the stored position;

FIG. 81 is a schematic view similar to FIG. 80 when the arcuate pawl driving wall has been rotated 178° toward the inhalation position; and

FIG. 82 is a schematic view similar to FIG. 80 in the inhalation position.

FIG. 83 is a top plan view of the base according to another embodiment of the metered powder dose dispenser of FIG. 1;

FIG. 84 is a bottom plan view of the base of FIG. 83;

FIG. 85 is a front elevational view of the base of FIG. 83;

FIG. 86 is a side elevational view of the base of FIG. 83;

FIG. 87 is a cross-sectional view of the base of FIG. 83, taken along line 87—87 thereof;

FIG. 88 is a bottom plan view of the lower spring retainer according to another embodiment of the metered powder dose dispenser of FIG. 1;

FIG. 89 is a top plan view of the lower spring retainer of FIG. 88;

FIG. 90 is a side elevational view of the lower spring retainer of FIG. 88;

FIG. 91 is a cross-sectional view of the lower spring retainer of FIG. 88, taken along line 91—91 thereof;

FIG. 92 is a cross-sectional view of the lower spring retainer of FIG. 88, taken along line 92—92 thereof;

FIG. 93 is a top plan view of the continuous counter ring according to another embodiment of the metered powder dose dispenser of FIG. 1;

FIG. 94 is a bottom plan view of the continuous counter ring of FIG. 93;

FIG. 95 is a cross-sectional view of the continuous counter ring of FIG. 93, taken along line 95—95 thereof;

FIG. 96 is a cross-sectional view of the continuous counter ring of FIG. 93, taken along line 96—96 thereof;

FIG. 97 is a side elevational view of the continuous counter ring of FIG. 93;

FIG. 98 is a top plan view of the intermittent counter ring according to another embodiment of the metered powder dose dispenser of FIG. 1;

FIG. 99 is a bottom plan view of the intermittent counter ring of FIG. 98;

FIG. 100 is a cross-sectional view of the intermittent counter ring of FIG. 98, taken along line 100—100 thereof;

FIG. 101 is a side elevational view of the intermittent counter ring of FIG. 98;

FIG. 102 is a perspective view of the pawl assembly according to another embodiment of the metered powder dose dispenser of FIG. 1;

FIG. 103 is a top plan view of the pawl assembly of FIG. 102;

FIG. 104 is a side elevational view of the pawl assembly of FIG. 102; and

FIG. 105 is a top plan view of a pawl assembly having an S-shaped spring according to another embodiment of the present invention, in which the pawl assembly is assembled with the base and the counter rings, but with the spring detents on the base omitted.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

Referring to the drawings in detail, and initially to FIGS. 1–4 thereof, a metered powder dose dispenser 10 according to the present invention includes a powder housing 20 for holding a supply of powdered material to be dispensed, and for supplying metered doses of the powder to a user.

Powder housing 20 is comprised of a reservoir body 22, a reservoir plug 90 and a driving body 120, each being formed as a single molded plastic piece.

Referring to FIGS. 3–8, reservoir body 22 includes a circular top wall 24 having an annular skirt 26 extending downwardly from the periphery of circular top wall 24. Annular skirt 26 includes an upper annular skirt section 28 with its upper end extending downwardly from the periphery of circular top wall 24, and a lower annular skirt section 30 extending downwardly from the lower end of upper annular skirt section 28. Lower annular skirt section 30 has an inner and outer diameter greater than the inner and outer diameters, respectively, of upper annular skirt section 28. Accordingly, an outer annular shoulder 32 is formed at the upper end of lower annular skirt section 30.

Diametrically opposite, axially extending drive slots 34 and 36 are formed in annular skirt 26, each extending for a different circumferential angular extent about annular skirt 26. For example, drive slot 34 is shown to extend along a 30° arc circumferentially of annular skirt 26, while drive slot 36 is shown to extend along a 40° arc circumferentially of annular skirt 26. Of course, the present invention is not limited to these particular angles. Drive slots 34 and 36 are open at their lower ends 38 and 40, respectively, and extend upwardly entirely through lower annular skirt portion 30 and partially through upper annular skirt portion 28. Thus, drive slots 34 and 36 have closed upper ends which define seating edges 42 and 44.

Powder housing 28 includes an arcuate manifold 46 formed on the upper surface of circular top wall 24, at a peripheral position offset from the center thereof. Manifold 46 includes an arcuate chamber 47 extending circumferentially for an arcuate length of approximately 140° about a peripheral portion of circular top wall 24 and which is defined by a surrounding chamber wall 48. Specifically, chamber wall 48 is formed by a lower chamber wall portion 50 extending upwardly from circular top wall 24 and an upper chamber wall portion 52 extending upwardly from the upper end of lower chamber wall portion 50. The shapes of

wall portions 50 and 52 are substantially identical, but with the inner dimensions of upper wall portion 52 being less than the inner dimensions of lower wall portion 50. As a result, a shoulder 54 is formed at the lower end of upper chamber wall portion 52.

Circular top wall 24 includes an opening 55 of the same shape and dimensions as lower chamber wall portion 50 of manifold 46 and in alignment with the lower end of lower chamber wall portion 50. The upper end of manifold 46, and particularly upper chamber wall portion 52, is closed by a manifold top wall 56 which is angled downwardly from the center thereof and which has an opening 58 at the center thereof.

A powder supply conduit 60 is formed on manifold top wall 52 at the center thereof in alignment with opening 58. The upper end of powder supply conduit 60 is open. Powder supply conduit 60 is normally filled with powder 62 for inhalation. As used herein, the terms "powdered medicaments" and "powder" include micronized powder, spheronized powder, micro-encapsulated powder, powder agglomerates and the like, and are used interchangeably with these terms herein.

A frusto-conical inhalation venturi conduit 64 is also formed on circular top wall 24 substantially parallel to powder supply conduit 60 and axially offset from the central axis of circular top wall 24. The center axis of powder supply conduit 60 and the center axis of venturi conduit 64 lie on a circle having a center coincident with the center of circular top wall 24, so as to be positioned at a peripheral portion of circular top wall 24, the center axes of conduits 60 and 64 being spaced apart along such a circle by an angle of approximately 105°.

Specifically, venturi conduit 64 is formed by a lower venturi conduit section 66 and an upper venturi conduit section 68 axially aligned therewith, each reducing in inner diameter from a lower end thereof to an upper end thereof. The upper end of upper venturi conduit section 68 is open, and upper venturi conduit section 68 has a smaller diameter than lower venturi conduit section 66 so that an inner annular shoulder 70 is formed at the lower edge of upper venturi conduit section 68. Circular top wall 24 includes a further opening 72 of the same shape and dimensions as the lower end of lower venturi conduit section 66 and in alignment therewith.

A peripheral securing wall 74 extends generally about a circular arc on a peripheral portion of circular top wall 24, in surrounding relation to lower chamber wall portion 50 and lower venturi conduit section 66. A gap 76 is provided in securing wall 74 at a position opposite conduits 60 and 64, and two parallel, spaced apart, radially extending tabs 78 extend inwardly from opposite ends of securing wall 74 at gap 76. Further, a radially extending annular lip 80 extends outwardly from the upper end of securing wall 74.

As will be understood from the description hereinafter, it is necessary that the lower surface of circular top wall 24 be as smooth as possible, that is, with very few undulations therein. However, this is difficult to achieve when molding reservoir body 22 as a single piece. Therefore, to overcome this problem, a reservoir plug 90 is provided, as shown in FIGS. 3, 4 and 9–13.

Specifically, reservoir plug 90 includes a thin circular plate 92 which can be molded, because of the thinness of plate 92, to have a very smooth lower surface with no undulations. The outer diameter of circular plate 92 is substantially equal to the inner diameter of upper annular skirt portion 28 so that reservoir plug 90 can be fit therein, as shown in FIG. 4. In such condition, the lower surface of circular plate 92 effectively is flush with seating edges 42 and 44 of drive slots 34 and 36.

Circular plate 92 has a circular hole 94, a first substantially oval hole 96 and a second substantially oval hole 98, all having centers extending along an imaginary circle centered at the center of plate 92.

A circular plug conduit 100 is formed on the upper surface of circular plate 92 in surrounding relation to circular hole 94. Conduit 100 is open at its upper and lower ends and has an outside diameter and a height substantially equal to the inside diameter and height, respectively, of lower venturi conduit section 66 and an inside diameter equal to the inside diameter of upper venturi conduit section 68. Thus, when reservoir plug 90 is inserted within upper annular skirt section 28, plug conduit 100 fits snugly within lower venturi conduit section 66 and the inner surface of plug conduit 100 forms a smooth continuation of the inner surface of upper venturi conduit section 68. In such condition, the upper edge of plug conduit 100 abuts against annular shoulder 70 so that no gap is formed between plug conduit 100 and upper venturi conduit section 68.

An arcuate plug conduit 102 is formed on the upper surface of circular plate 92 in surrounding relation to first and second substantially oval holes 96 and 98. Plug conduit 102 has the same shape as lower chamber wall portion 50 of manifold 46. Plug conduit 102 is open at its upper and lower ends and has an outside shape and dimensions substantially equal to the inside shape and dimensions, respectively, of lower chamber wall portion 50, inside shape and dimensions equal to the inside shape and dimensions of upper chamber wall portion 52, and a height equal to the height of lower chamber wall portion 50. Thus, when reservoir plug 90 is inserted within upper annular skirt section 28, plug conduit 102 fits snugly within lower chamber wall portion 50 and the inner surface of plug conduit 102 forms a smooth continuation of the inner surface of upper chamber wall portion 52. In such condition, the upper edge of plug conduit 102 abuts against shoulder 54 so that no gap is formed between plug conduit 102 and upper chamber wall portion 52.

Although the outer surfaces of plug conduits 100 and 102 are discussed above as being smooth, it will be appreciated that such outer surfaces can be formed with ribs 104, as shown in FIGS. 4, 12 and 13.

As shown in FIGS. 3, 4 and 14–21, driving body 120 includes a circular top wall 122 having an annular skirt 124 extending downwardly from the periphery of circular top wall 122.

Annular skirt 124 includes an upper annular skirt section 126 with its upper end extending downwardly from the periphery of circular top wall 122, and a lower annular skirt section 128 extending downwardly from the lower end of upper annular skirt section 126. Lower annular skirt section 128 has an inner and outer diameter greater than the inner and outer diameters, respectively, of upper annular skirt section 126. Accordingly, an inner annular shoulder 130 is formed at the lower edge of upper annular skirt section 126, along the inside of annular skirt 126. However, the outer surface of the transition area between upper annular skirt section 126 and lower annular skirt section 128 is formed as a frusto-conical surface 132.

Further, the inner diameter of lower annular skirt section 128 is substantially the same as the outer diameter of upper annular skirt section 28 of reservoir body 22 and the inner diameter of upper annular skirt section 126 is substantially the same as the outer diameter of peripheral securing wall 74

of reservoir body 22. Accordingly, reservoir body 22 fits into driving body 120 with a close fit until the radially extending annular lip 80 of peripheral securing wall 74 abuts against annular shoulder 130.

In order to lock reservoir body 22 and driving body 120 together in such position, two axially spaced apart, circumferentially extending ribs 134 and 136 are formed parallel to and spaced above annular shoulder 130, on the inner surface of upper skirt section 126, to define an annular holding area 138 therebetween. Thus, when reservoir body 22 is inserted within driving body 120 in the manner described above, lip 80 at the upper end of peripheral securing wall 74, due to the resilience of the plastic pieces, rides along the inner surface of upper skirt portion 126 and over lower rib 136, and is held between ribs 134 and 136 within annular holding area 138.

Further, to ensure proper orientation between reservoir body 22 and driving body 120, two spaced apart, axially extending, radially oriented aligning ribs 140 are provided on the inner surface of upper annular skirt section 126. Ribs 140 are spaced apart by a distance substantially equal to the width of gap 76. Thus, in the assembled condition of reservoir body 22 and driving body 120, ribs 140 fit with close tolerance between tabs 78 of reservoir body 22, that is, within gap 76.

Circular top wall 122 is formed with a circular opening 142 which is aligned with and receives frusto-conical venturi conduit 64 so that the upper edge of frusto-conical venturi conduit 64 is substantially flush with the upper surface of circular top wall 122.

A circular plug conduit 144 depends downwardly from the lower surface of circular top wall 122 and is in alignment with powder supply conduit 60. A radially extending rib 146 extends outwardly from the lower end of plug conduit 144 and has an outer diameter substantially equal to or slightly greater than the inside diameter of powder supply conduit 60. Thus, plug conduit 144 closes the upper open end of powder supply conduit 60 when reservoir body 22 is assembled with driving body 120. Therefore, powder 62 can only escape through manifold 46, opening 55 and substantially oval holes 96 and 98.

Further, a curved retaining wall 148 extends downwardly from the lower surface of circular top wall 122 in partial surrounding relation to circular opening 142 to ensure a further separation between powder supply conduit 60 and frusto-conical venturi conduit 64 when reservoir body 22 and driving body 120 are assembled.

In order to provide for secondary air flow, as will be described hereinafter, the wall defining upper annular skirt section 126 extends inwardly in the radial direction to form a first outer air passage 150 adjacent to circular opening 142 in the circumferential direction of driving body 120 and a second outer air passage 152 arcuately spaced approximately 100° from first air passage 150.

Axially extending upper securing walls 154, 156 and 158 are formed along a common circular arc at the periphery on the upper surface of circular top wall 122 in order to secure a nozzle to driving body 120, as will be described in greater detail hereinafter. Specifically, upper securing wall 154 is formed circumferentially between air passages 150 and 152; upper securing wall 156 is formed circumferentially between second outer air passage 152 and plug conduit 144; and upper securing wall 158 is formed circumferentially between first outer air passage 152 and plug conduit 144 and in outer surrounding relation to circular opening 142. A radially extending rib 160 extends outwardly from the upper end of each upper securing wall 154, 156 and 158. The common circular arc along which upper securing walls 154, 156 and 158 extend is spaced slightly from the peripheral edge of circular top wall 122 so as to define an annular retaining ledge 159 on circular top wall 122, positioned outwardly of upper securing walls 154, 156 and 158 in the radial direction.

A rotation limiting tab 162 is formed in downwardly depending relation from the lower edge of lower annular skirt section 128, the purpose for which will be apparent from the description hereinafter. Rotation limiting tab 162 includes a rounded nub 163 at the lower end thereof.

Lastly, two diametrically opposite driving recesses 164 and 166 are formed in lower annular skirt section 128, with driving recess 164 being in circumferential alignment with circular opening 142. As will be described hereinafter, driving recesses 164 and 166 are engaged to rotate driving body 120.

In order to provide metered doses of powder 62 from powder supply conduit 60 to venturi conduit 64, a metering dose plate 180 is positioned within upper annular skirt section 28 of reservoir body 22, immediately below reservoir plug 90. Specifically, metering dose plate 180 includes a thin disc 182 having a single small metered dose hole 184 near the periphery thereof which functions as a single powder receptacle, that is, for holding a metered dose of powder 62. In order to prevent the metered dose of powder from falling through dose hole 184, a powder retainer 186 is formed in covering relation to the lower surface of disc 182, extending at least over dose hole 184. Preferably, powder retainer 186 is formed by a mesh screen, filter, porous material or the like which has a minimal restrictive effect on gas flow therethrough, while preventing appreciable loss of powdered medicament below the lower surface of disc 182. Powder retainer 186' can be fabricated from any suitable material, including cellulosics, polymerics, metals, ceramics, glasses or composites thereof, exemplary useful materials including sintered porous plastics, porous polymer membranes, natural or synthetic woven fabrics, nonwoven synthetic fabrics and the like. More specifically, useful materials include polyester and polyolefin woven mesh, and porous membranes of polyolefins, polycarbonates, polytetrafluoroethylene, polyvinylidene dichloride, and mixed esters of cellulose.

An annular mounting post 188 extends downwardly from the lower surface of disc 182 and is centrally located thereon. Annular mounting post 188 is formed with a flat 190 along the length thereof, flat 190 extending an arcuate distance of approximately 65°. As will be understood from the description hereinafter, flat 190 ensures that metering dose plate 180 will remain stationary with respect to powder housing 20 when powder housing 20, which includes reservoir body 22, reservoir plug 90 and driving body 120, is rotated.

In operation, metered dose hole 184 is initially in alignment with frusto-conical venturi conduit 64. As will be explained hereinafter, powder housing 20 is only permitted to rotate 180° relative to metering dose plate 180. During initial priming rotation, metered dose hole 184 passes under manifold 46 and substantially oval holes 96 and 98. As a result, powder 62 falls within and is scraped into metered dose hole 184. Specifically, the side walls defining substantially oval holes 96 and 98 function to scrape the powder 62 into metered dose hole 184. It will be appreciated that, since oval holes 96 and 98 are spaced less than 180° from circular hole 94, metered dose hole 184 travels completely past oval holes 96 and 98 and manifold 46. Then, during the return

rotation back to the initial position, metered dose hole **184** passes back under manifold **46** and substantially oval holes **96** and **98**, into alignment with venturi conduit **64**. During this return travel, the side walls defining substantially oval holes **96** and **98** again function to scrape the powder **62** into metered dose hole **184**, thus ensuring that metered dose hole **184** is completely and accurately filled. Thus, the scraping action is provided during both counterclockwise and clockwise rotation, that is, both during the 180° loading stage and the reverse 180° movement to the inhalation stage. When metered dose hole **184** is aligned with venturi conduit **64**, it is then only necessary for the user to inhale through venturi conduit **64**, causing a draw and suction through metered dose hole **184**, wherein the metered dose of powder **62** is drawn up through venturi conduit **64** and delivered to the user.

In order to provide for this relative rotation, metering dose plate **180** is non-rotatably mounted on, and powder housing **20** is rotatably mounted on, a base **200**, shown in FIGS. **3**, **4** and **25–29**. Base **200** includes a circular top wall **202** having an annular skirt **204** extending downwardly from the periphery thereof. The peripheral edge of circular top wall **202** is cut-away to define an outer annular ledge **206**. An annular supporting lip **208** is formed on the outer surface of annular skirt **204** at the lower end thereof, so as to extend outwardly therefrom in the radial direction of annular skirt **204**. In addition, an annular retaining rim **210** is formed on the outer surface of annular skirt **204**, parallel to supporting lip **208** and spaced thereabove, so as to extend outwardly from annular skirt **204** in the radial direction thereof. Retaining rim **210** has a diameter less than the diameter of supporting lip **208**. Thus, an annular retaining gap **212** is formed between supporting lip **208** and retaining rim **210**. Further, retaining rim **210** is cut away along a very small arcuate distance to define a small slot **214** therein, and also has a frusto-conical upper annular surface.

A cylindrical boss **216** is formed centrally and axially on the upper surface of circular top wall **202**, and a coaxial retaining post **218** of lesser diameter than cylindrical boss **216** is formed at the upper end of cylindrical boss **216**. Accordingly, an outer annular ledge **220** is formed at the upper edge of cylindrical boss **216**. Retaining post **218** has an outer diameter slightly less than the inner diameter of annular mounting post **188** of metering dose plate **180**. Retaining post **218** is formed with a flat **222** along the length thereof, flat **222** extending an arcuate distance of approximately 65°. Accordingly, due to flats **190** and **222**, mounting post **188** of metering dose plate **180** is retained on retaining post **218** in a non-rotatable manner to ensure that metering dose plate **180** will remain stationary with respect to powder housing **20** when powder housing **20**, which includes reservoir body **22**, reservoir plug **90** and driving body **120**, is rotated.

As part of a counter mechanism which will be described in greater detail hereinafter, a first rotation prevention spring detent **224** is mounted in a cantilever manner on circular top wall **202**. Specifically, a curved vertical detent supporting wall **226** extends upwardly from circular top wall **202** at a position substantially midway between annular ledge **206** and cylindrical boss **216**, and first rotation prevention spring detent **224** extends from one edge **228** of detent supporting wall **226**, parallel to and spaced above circular top wall **202**. Further, the free end of first rotation prevention spring detent **224** is provided with a bevel **230** thereat which is oriented in the radial direction of circular top wall **202**.

Also as part of the counter mechanism which will be described in greater detail hereinafter, a second rotation prevention spring detent **232** is mounted in a cantilever manner on circular top wall **202**. Specifically, second rotation prevention spring detent **232** extends from edge **228** of detent supporting wall **226**, parallel to and spaced above circular top wall **202** and parallel to and spaced above first rotation prevention spring detent **224**. The free end of second rotation prevention spring detent **232** is provided with a bevel **234** thereat which is oriented in the radial direction of circular top wall **202**. It is noted particularly from FIG. **25** that the free end of detent **224** extends radially outward to a slightly greater extent than the free end of detent **232**.

A sectored recess **236** is formed in circular top wall **202** in correspondence with detents **224** and **232**. Specifically, recess **236** includes a first radial boundary **238** in line with the free end of detent **232**, a second radial boundary **240** in line with the connected end of detent **232**, and a third boundary **242** connected between the inner ends of radial boundaries **238** and **240** and extending in alignment with the lengthwise direction of detent **232**.

In order to spring bias metering dose plate **180** into engagement with the lower surface of thin circular plate **92** of reservoir plug **90** and to ensure that powder **92** can only be inhaled when metered dose hole **184** is in alignment with venturi conduit **64**, a biasing assembly is provided.

The biasing assembly includes a lower spring retainer **260** mounted on annular ledge **220**, over retaining post **218**, as shown in FIGS. **3**, **4** and **30–34**. Specifically, lower spring retainer **260** includes a disc **262** having a central opening **264** sized to receive retaining post **218**. An annular boss **266** extends from the lower surface of disc **262** in surrounding relation to central opening **264**. When retaining post **218** extends through annular boss **266** and central opening **264**, the lower edge of annular boss **266** seats upon annular ledge **220**.

An upper annular retaining lip **268** extends upwardly from the peripheral edge of disc **262**. Further, two radially extending driven ears **270** and **272** are formed in diametrically opposite positions at the peripheral edge of annular lip **268**. Ear **270** has a width substantially equal to the width of drive slot **34** of reservoir body **22** so as to fit therein and be driven thereby, and ear **272** has a width substantially equal to the width of drive slot **36** of reservoir body **22** so as to fit therein and be driven thereby.

Further, an arcuate pawl driving wall **274** extends from the lower surface of disc **262** between annular boss **266** and the periphery of disc **262**, for an arcuate distance of approximately **790**. Pawl driving wall **274** includes opposite pawl driving ends **276** and **278**, as will be described in greater detail hereinafter with reference to the counter mechanism.

The biasing assembly further includes a coil spring **290** having one end seated on the upper surface of disc **262** of lower spring retainer **260**, and restrained thereon by annular retaining lip **268**.

As shown in FIGS. **3**, **4** and **35–37**, the biasing assembly further includes a support plate **300** which supports metering dose plate **180**, functions as an upper spring retainer, biases metering dose plate **180** against the lower surface of thin circular plate **92** of reservoir plug **90**, and permits suction through metered dose hole **184** only when metered dose hole **184** is in alignment with venturi conduit **64**.

Specifically, support plate **300** is formed by a disc **302** having an annular retaining lip **304** extending downwardly from the peripheral edge of disc **302**.

Two radially extending driven ears **306** and **308** are formed in diametrically opposite positions at the peripheral

edge of annular lip **304**. Ear **306** has a width substantially equal to the width of drive slot **34** of reservoir body **22** so as to fit therein and be driven thereby, and ear **308** has a width substantially equal to the width of drive slot **36** of reservoir body **22** so as to fit therein and be driven thereby. The height of ears **306** and **308** is less than the height of annular lip **304**, and lower surfaces of ears **306** and **308** are substantially flush with the lower edge of annular lip **304**, although the invention is not so limited.

In addition, a central circular hole **310** is formed in disc **302** and is sized to rotatably receive annular mounting post **188** of metering dose plate **180** therein. A radially extending slot **312** extends from and is in communication with circular hole **310**. Slot **312** extends outwardly in the radial direction by a distance such that the radially outer part of slot **312** overlaps metered dose hole **184** when metered dose hole **184** is in alignment with venturi conduit **64**, and is out of alignment with, and thereby does not overlap, metered dose hole **184** at all other times.

As described above, powder retainer **186** is formed by a mesh screen, filter, porous material or the like which has a minimal restrictive effect on gas flow therethrough. However, when a mesh screen or the like is used, there is a reduction in gas flow, and thereby of any suction by the user, of approximately 35%. According to an alternative embodiment, as shown in FIG. **38**, powder retainer **186** comprised of a mesh screen or the like can be relocated to the lower surface of disc **302** of support plate **300**, under slot **312**. Therefore, although the mesh screen or the like reduces the gas flow through radially extending slot **312**, this does not effectively restrict the gas flow through metered dose hole **184** which is smaller than slot **312**. Thus, primary air flow is independent of the cross-sectional width of metering dose plate **180**. Further, there is no mesh powder retainer **186** at metered dose hole **184** to reduce air flow through metered dose hole **184**.

As shown in FIG. **39**, which is an alternative embodiment of the arrangement of FIG. **38**, slot **312** in support plate **300** is angled at opposite sides thereof in a downwardly diverging manner. With such arrangement, the air flow cross-sectional area at the bottom of slot **312** can be made greater than four times the air flow cross-sectional area of metered dose hole **184**.

It will be appreciated from the above description that metering dose plate **180** is held stationary on base **200**, due to flats **190** and **222**. Further, powder housing **20**, comprised of reservoir body **22**, reservoir plug **100** and driving body **120**, is rotatably mounted with respect to base **200** and metering dose plate **180**.

In addition, support plate **300** is biased into engagement with the lower surface of metering dose plate **180** so as to support the same. In the operation, radially extending slot **312** is in alignment with metered dose hole **184** only when metered dose hole **184** is in alignment with venturi conduit **64**. Thus, any powder **62** within metered dose hole **184** when metered dose hole **184** is out of alignment with venturi conduit **64** is sandwiched in metered dose hole **184** by mesh powder retainer **186** and the upper surface of disc **302** of support plate **300** at its lower end, and by the lower surface of thin circular plate **92** of reservoir plug **90** at its upper end. As will be discussed in greater detail hereinafter, in the stored or inactive position of metered powder dose dispenser **10**, metered dose hole **184** is primed, and is positioned diametrically opposite to radially extending slot **312**. In such position, powder **62** within metered dose hole **184** is held between the upper surface of disc **302** of support plate **300** and the lower surface of thin circular plate **92** of reservoir plug **90**, and therefore cannot escape metered dose hole **184**.

In order to positively hold all of the above elements together, metered powder dose dispenser **10** further includes an adapter **320**, as shown in FIGS. **3**, **4** and **40–45**. As shown therein, adapter **320** includes a lower annular wall **322** having an inner diameter larger than the outer diameter of lower annular skirt section **30** of reservoir body **22** so as to easily fit thereover. The inner diameter of lower annular wall **322** is also slightly larger than the outer diameter of annular skirt **204** of base **200** so as to fit thereover, but slightly less than the outer diameter of annular retaining rim **210** of base **200**. Further, the inner, lower edge of lower annular wall **322** is beveled at **323**.

An annular groove **324** is formed at the lower end of lower annular wall **322**, slightly spaced above the lower edge thereof. Accordingly, due to the resilience of the plastic pieces, when adapter **320** is inserted over base **200** and pushed down thereon, retaining rim **210** of base **200** snaps into annular groove **324** to hold adapter **320** on base **200**. In order to obtain and maintain correct alignment between adapter **320** and base **200**, adapter **320** is provided with a small bridge **326** within groove **324**. Bridge **326** has a width substantially equal to that of small slot **214** in base **200** so as to fit therein. Thus, rotation of adapter **320** causes base **200** to rotate therewith.

The outer surface of lower annular wall **322** is preferably provided with a gripping surface **328** formed by undulations, knurling or the like, to enhance the gripping and rotation of metered powder dose dispenser **10**.

An oval transparent plastic window **330** is provided in lower annular wall **322**, substantially diametrically opposite to bridge **326**, and substantially centrally along the height of lower annular wall **322** for use with the counter mechanism which will be described in greater detail hereinafter.

Adapter **320** further includes an upper annular wall **332** of a lesser diameter than lower annular wall **322**, and connected to the upper end of lower annular wall **322** by an annular frusto-conical connecting section **334**. As will be apparent from the description hereinafter with respect to the counter mechanism, a dosage limiter tab **336** is formed above window **330** on the inner surfaces of connecting section **334** and lower annular wall **322**. Dosage limiter tab **336** prevents operation of metered powder dose dispenser **10** after a prescribed number of doses, for example **200** doses, have been dispensed; this is sometimes referred to herein as a "lock-out" feature.

An annular biasing lip **338** is formed on the inner surface of upper annular wall **332**. When adapter **320** is pushed down so as to lock adapter **320** onto base **200**, as described above, annular biasing lip **338** seats on outer annular shoulder **32** of reservoir body **22**, and thereby biases reservoir body **22** down against the force of coil spring **290**. Accordingly, coil spring **290** is compressed so that a biasing force always forces support plate **300** into abutment with metering dose plate **180**, and always forces metering dose plate **180** into abutment with reservoir plug **90**. However, such biasing action still permits rotation of reservoir body **22** relative to adapter **320** and metering dose plate **180**.

At the same time, this compression ensures that driven ears **270** and **306** will always be located within drive slot **34** and driven ears **272** and **308** will always be located within drive slot **36**, so that rotation of reservoir body **22** will cause consequent rotation of lower spring retainer **260** and support plate **300**. Because metering dose plate **180** is held stationary on base **200**, due to flats **190** and **222**, powder housing **20**

(comprised of reservoir body 22, reservoir plug 100 and driving body 120), lower spring retainer 260 and support plate 300, are rotatably mounted with respect to base 200, metering dose plate 180 and adapter 320.

In the assembled condition discussed above, the lower edge of lower annular skirt section 128 of driving body 120 rests and rotates on the upper edge of upper annular wall 332 of adapter 320. In order to provide air flow through metered dose hole 184 of metering dose plate 180, two diametrically opposite recesses 340 and 342 are formed in upper annular wall 332, extending from the upper edge of upper annular wall to annular biasing lip 338. Recess 340 has a width identical to the width of drive slot 34, while recess 342 has a width identical to the width of drive slot 36. When metered dose hole 184 is aligned with venturi conduit 64 of reservoir body 22 and with radially extending slot 312 of support plate 300, recess 340 is in alignment with drive slot 34 and recess 342 is in alignment with drive slot 36. Accordingly, suction on venturi conduit 64 causes air to flow through recess 340 and drive slot 36 and through recess 342 and drive slot 36, and then through radially extending slot 312, metered dose hole 184 and venturi conduit 64 to deliver the metered dose of powder 62 in metered dose hole 184, to a user of dispenser 10.

When the lower edge of lower annular skirt section 128 of driving body 120 rests and rotates on the upper edge of upper annular wall 332 of adapter 320, rotation limiting tab 162, and rounded nub 163 thereof, ride along the upper surface of annular biasing lip 338. In this regard, two stops 344 and 346 are formed on the upper surface of annular biasing lip 338 such that opposite ends of rotation limiting tab 162 abut thereagainst during rotation of driving body 120 relative to adapter 320, in order to limit rotation of powder housing 20 to a clockwise and counterclockwise rotation of 180°.

In order to prevent accidental rotation of driving body 120 relative to adapter 320, two detents 348 and 350 of a small height are provided on the upper surface of annular biasing lip 338, slightly spaced from stops 344 and 346, respectively. Accordingly, during rotation of driving body 120 relative to adapter 320, rounded nub 163 at the lower end of rotation limiting tab 162 is caused to ride over detents 348 and 350 due to resilience of the plastic parts. Rotation limiting tab 162 is thereby releasably held between stop 344 and detent 348, or releasably held between stop 346 and detent 350.

Lastly, a double helical thread 352 is formed on the outer surface of upper annular wall 332, the purpose for which will become apparent from the description which follows.

In order to ensure that the powder is de-agglomerated and properly mixed with the suction air from the open upper end of upper venturi conduit section 68 of venturi conduit 64, a swirl nozzle 380 is mounted to the upper end of reservoir body 22. Air which contains agglomerated powder particles flows from upper venturi conduit section 68 into the swirl nozzle. Mechanical de-agglomeration is an important function of the swirl nozzle.

Swirl nozzle 380 includes a circular top wall 382 and an annular side wall 384 extending downwardly from the periphery of top wall 382. Annular side wall 384 has an outer diameter substantially equal to the outer diameter of upper annular skirt section 126 of driving body 120. Further, the inner connecting region 386 between circular top wall 382 and annular side wall 384 is curved to provide a smooth transition therebetween and thereby to provide a smooth flow path for powder 62. In other words, the inner area defined by circular top wall 382, annular side wall 384 and inner connecting region 386 has a somewhat partial toroidal configuration. The outer connecting region 390 therebetween, however, forms a substantially right angle in cross-section between circular top wall 382 and annular side wall 384.

In order to secure swirl nozzle 380 onto the upper end of driving body 120, and particularly, onto annular retaining ledge 159 of driving body 120, three recessed sections 392, 394 and 396 are formed on the inner surface of annular side wall 384. Recessed sections 392, 394 and 396 extend arcuate distances which are different from each other and which correspond identically with the arcuate distances of upper securing walls 154, 156 and 158 of driving body 120. Further, recessed sections 392, 394 and 396 are spaced apart in an identical manner to upper securing walls 154, 156 and 158 of driving body 120.

Each recessed section 392, 394 and 396 includes a lower arcuate cut-away area 398 that extends upwardly along the inner surface of annular side wall 384 from the lower edge thereof. Thus, each cut-away area 398 has a wall thickness less than the wall thickness of annular side wall 384 at positions outside of recessed sections 392, 394 and 396. Each recessed section 392, 394 and 396 further includes an upper arcuate groove 400 formed by cutting away an area of each recessed section 392, 394 and 396 immediately above cut-away area 398. In other words, each arcuate groove 400 is formed so that the wall thickness of annular side wall 384 thereat is less than the wall thickness of cut-away area 398.

It will therefore be appreciated that swirl nozzle 380 is snap fit onto driving body 120. Specifically, recessed sections 392, 394 and 396 are aligned with upper securing walls 154, 156 and 158 of driving body 120. When a downward axial force is applied to swirl nozzle 380, and due to the resilience of the plastic elements, radially extending ribs 160 of upper securing walls 154, 156 and 158 ride over cut-away areas 398 and into arcuate grooves 400, so as to retain swirl nozzle 380 on driving body 120. It will be appreciated that, in such position, first and second outer air passages 150 and 152 extend inwardly of annular side wall 384 to supply secondary air flow thereto which mixes with the air/powder mixture from venturi conduit 64 which is also supplied to the interior of annular side wall 384.

Circular top wall 384 has a central opening 402, and a supply chimney 404 is formed on the upper surface of circular top wall 384 in surrounding relation to central opening 402.

In order to break up the powder agglomerates, prior to supplying the same through supply chimney 404, a curved spiral-like wall 406 extends downwardly from circular top wall 382 and is connected at one end 408 to annular side wall 384. Specifically, curved wall 406 extends in a curvilinear manner from end 408, and partially about central opening 402 to an opposite end 410. Thus, a gap 409 is provided between end 410 and the remainder of curved wall 406. The height of curved wall 406 is equal to that of annular side wall 384 so that the lower edge of curved wall 406 sits on circular top wall 122 of driving body 120 when swirl nozzle 380 is assembled with driving body 120, as described above. Curve wall 406 is effectively formed in two sections, namely, a first section 406*a* extending partially about central opening 402, for example, for 165°, and a second section 406*b* extending from one end of first section 406*a* to the inner surface of annular side wall 384 along a larger radius than first section 406*a*. With respect to the direction of the radius to the center of venturi conduit 64, second section 406*b* preferably leaves

or disengages from central opening **402** at an angle of approximately 150 parallel to such radius line, regardless of the size of swirl nozzle **380**.

As will be appreciated, curved wall **406** defines a swirl cavity **412**, such that the powder from venturi conduit **64** enters swirl cavity **412** and continuously changes direction as it increases in velocity, prior to entering supply chimney **404**. Thus, the powder agglomerates constantly impact against circular top wall **382**, annular side wall **384** and curved wall **406** within swirl cavity **412**. Further, the agglomerates collide with each other which results in a mutual grinding or shattering action between the agglomerates. At the same time, secondary air flow from first and second outer air passages **150** and **152** enters swirl chamber **412**, as indicated by arrows **414** and **416**, respectively, to accelerate movement of the powder agglomerates in swirl cavity **412**. The constant impacts of the powder agglomerates on the walls defining swirl cavity **412** cause the agglomerates to break up into micronized powder upon impact. Basically, as long as the powder agglomerates travel with sufficient velocity, there will be sufficient kinetic energy to break up the agglomerates.

Further, rather than providing a merely helical path along the axial direction of a nozzle, as in the prior art, curved wall **406** and, particularly, swirl cavity **412**, first changes the direction of powder **62** from an axial direction of venturi conduit **64** to a transverse direction substantially perpendicular to the axial direction. In this transverse direction, powder **62** is then forced to continuously change direction in the transverse direction of swirl cavity **412**. Upon exiting swirl cavity **412**, the direction of powder **62** is again changed to an axial direction through supply chimney **404**, while retaining a swirl component of the flow, that is, while swirling spirally through chimney **404**. Since the micronized powder and any remaining agglomerates maintain the swirl imparted thereto from swirl cavity **412**, the swirling flow applies a centrifugal force to the micronized powder and remaining agglomerates, creating additional impacts in supply chimney **404** so as to result in further breaking up of the remaining agglomerates.

Most of the agglomerate break-up should take place, however, in swirl cavity **412**. The velocity attained by an agglomerate depends on the drag or suction force, the inertia of the agglomerate, and the length of swirl cavity **412**, that is, the time the drag force acts on the agglomerate. Because of its inertia, the agglomerate impacts a wall in swirl cavity **412** to convert the same to micronized powder.

In addition to breaking up agglomerates, swirl nozzle **380** must meet additional constraints. For example, the pressure drop through the powder inhaler should desirably be lower than about 20 inches of a water column (5 Kpa) for ease of use by persons with impaired respiratory function, yet sufficiently high to permit significant primary air flow through metered dose hole **184**. The pressure drop through swirl nozzle **380** can be changed by varying the angle a between end **410** of first section **406***a* of curved wall **406** and the position where first section **406***a* and second section **406***b* of curved wall **406** meet, that is, where second section **406***b* leaves central opening **402**, as shown in FIG. **47**. In a presently preferred embodiment, α is about 165°, although this value may change depending upon the required pressure drop.

Further, an annular mouthpiece securing wall **418** is formed on the upper surface of circular top wall **382**, spaced slightly inwardly from the peripheral edge thereof. As a result, an annular ledge **420** is formed on the upper surface of circular top wall **382**, outwardly of annular mouthpiece securing wall **418**. Further, an annular lip **422** extends outwardly in the radial direction from the upper end of annular mouthpiece securing wall **418**.

A mouthpiece **440**, as shown in FIGS. **3**, **4** and **51–55**, is secured to the upper end of swirl nozzle **380**. Mouthpiece **440** includes a generally rectangular top wall **442** with an annular side wall **444** depending downwardly from the periphery of top wall **442**. Because top wall **442** has a generally rectangular configuration and because of the annular configuration of side wall **444**, upper portions at opposite sides **446** and **448** of side wall **444** corresponding to the lengthwise sides of top wall **442** slope upwardly in a diverging manner toward each other. The lips of a user of the device are placed on sides **446** and **448** during inhalation. Of course, since the user's mouth is placed over mouthpiece, the various edges thereof are rounded.

An opening **450** is centrally formed in top wall **442**, the upper part of which has a frusto-conical shape and the lower part of which has a circular shape, as shown in FIGS. **52** and **53**. An annular connecting tube **452** is formed at the lower surface of top wall **442** in surrounding relation to opening **450**. When mouthpiece **440** is seated on swirl nozzle **380**, connecting tube **452** receives the upper end of supply chimney **404** of swirl nozzle **380** therein.

In order to secure mouthpiece **440** to swirl nozzle **380**, the lower end of side wall **444** has a circular or annular shape. At the inner surface of this lower end of side wall **444**, there is formed an annular V-shaped projection **454** which extends inwardly in the radial direction. When mouthpiece **440** is positioned on swirl nozzle **380** and pressed down thereon, annular lip **422** of swirl nozzle **380**, due to resilience of the plastic pieces, rides over V-shaped projection **454**, so that V-shaped projection **454** retains annular lip **422**, and thereby mouthpiece **440**, on swirl nozzle **380**. In such position, the lower edge of side wall **444** sits on annular ledge **420** of swirl nozzle **380**.

An alternative embodiment of nozzle **380** and mouthpiece **440** is shown in the combination mouthpiece nozzle **480** shown in FIGS. **56–58**. Specifically, mouthpiece nozzle **480** includes an upper section **482** having a similar outer shape and dimensions to those of mouthpiece **440**. In this regard, upper section **482** of mouthpiece **480** includes a generally rectangular top wall **484** with a cylindrical side wall **486** depending downwardly from the periphery of top wall **484**. Because top wall **484** has a generally rectangular configuration and because of the annular configuration of side wall **486**, opposite sides **488** and **490** of side wall **486** corresponding to the lengthwise sides of top wall **484** slope upwardly in a diverging manner toward each other. The lips of a user of the device are placed on sides **488** and **490** during inhalation. Of course, since the user's mouth is placed over mouthpiece, the various edges thereof are preferably rounded.

Mouthpiece nozzle **480** further includes a lower section **492** formed at the lower end of upper section **482**. Lower section **492** includes a retaining groove **494** along the inner surface thereof, which serves the same purpose as upper arcuate groove **400** of swirl nozzle **380**. In other words, due to the resilience of the plastic elements, radially extending ribs **160** of upper securing walls **154**, **156** and **158** of driving body **120** are inserted within retaining groove **494**, so as to retain mouthpiece nozzle **480** on driving body **120**.

A swirl cavity **496** is formed inside of mouthpiece nozzle **480** at a position above retaining groove **494**. The interior surface contour of swirl cavity **496** resembles the shape of

an inverted tornado, as shown in FIG. **58**. Specifically, the interior surface contour is a continuously changing circle, the radius of which changes exponentially by depth from a lower outer circle of radius c_0+c_1 to an upper circle of radius c_0. The origin of the continuously changing circle is denoted by designators a and b which correspond to the x and y coordinates. This origin (a,b) itself moves in a circle which changes with depth. Therefore, not only does the radius change with depth, but also, the origin of the circle also changes with depth.

The equation for the interior surface contour is as follows:

$$(x-a)^2+(y-b)^2=c_0+c_1{}^*e^{-kz},$$

where

$a=a_0{}^*\text{sine}\ (a_1{}^*\pi)$ and

$b=b_0{}^*\text{cosine}\ (b_1{}^*\pi)$

The exponential coefficient k defines the geometry of the tornado spiral, and for an upper radius of approximately 6.35 mm (¼ inch) and a lower radius of approximately 25.4 mm (one inch), a value of k equal to 13 was found to operate satisfactorily.

It will be appreciated that the above equation is a variation on the general equation for a circle, that is $x^2+y^2=r$, where r is the radius of the circle. The additional terms at the left of the tornado equation take into account the changing center of the circle, while the additional terms at the right take into account the changing height or depth of the circle. Thus, for the initial height of z=0 at the lower, larger radius end of the interior surface contour, e^{-kz} equals 1, so that the right side of the equation reduces to c_0+c_1, which is the radius at the bottom of the interior surface contour. On the other hand, at the top, it is assumed that $z=\infty$, whereby $c_1{}^*e^{-kz}=0$, so that the radius at the upper end of the interior surface contour is equal to c_0.

With this arrangement, the outlet of venturi conduit **64** directly discharges into the tornado swirl cavity **496**. During travel therethrough, the agglomerates impact against the walls defining the interior surface contour of swirl cavity **496**, thereby breaking up the agglomerates into micronized powder.

It will be appreciated by those having skill in the art that the mouthpieces can readily be altered to permit nasal delivery of the medicaments, without changing the internal configuration and dimensions of the swirl nozzles. Only the exterior size and shape of the mouthpiece will require modification for nasal delivery.

Referring now to FIGS. **59–63**, a closure cap **520** of metered powder dose dispenser **10** is provided as a closure for mouthpiece **440**, and at the same time, functions to prime metered powder dose dispenser **10** for use. Specifically, closure cap **520** includes an upper elongated annular covering wall **522** which is closed at its upper end by a generally circular top wall **524**. A lower annular securing skirt **526** of a larger diameter than annular covering wall **522**, is secured to the lower end of annular covering wall **522** through an annular frusto-conical connector **528**. The lower end of annular securing skirt **526** is open. Further, the inner diameter of lower annular securing skirt **526** is slightly larger than the outer diameter of upper annular wall **332** of adapter **320** so as to fit thereover.

In order to secure closure cap **520** onto metered powder dose dispenser **10**, and particularly, in covering relation to mouthpiece **440**, a double helical thread **530** is formed on the inner surface of lower annular securing skirt **526**. Thus, when closure cap **520** is inserted over powder housing **20**, swirl nozzle **380** and mouthpiece **440**, helical thread **530** of closure cap **520** threadedly engages with double helical thread **352** of adapter **320**, until the lower edge of lower annular securing skirt **526** seats on the annular frusto-conical connecting section **334** of adapter **320**. It will be appreciated that the outer diameter of lower annular securing skirt **526** is substantially identical with the outer diameter of lower annular wall **322** of adapter **320** to provide a relative smooth, continuous appearance. In order to aid in the removal and closing of closure cap **520**, the outer surface of lower annular securing skirt **526** is formed with a gripping surface **532** formed by undulations, knurling or the like, to enhance the gripping and rotating of closure cap **520**.

As discussed above, closure cap **520** also serves to prime metered powder dose dispenser **10** for use. Specifically, a first pair of parallel, axially extending, spaced apart priming ribs **534** are formed on the inner surface of closure cap **520**, extending a small distance down from frusto-conical connector **528** onto lower annular securing skirt **526**. A second pair of parallel, axially extending, spaced apart priming ribs **536** are also formed on the inner surface of closure cap **520**, extending a small distance down from frusto-conical connector **528** onto lower annular securing skirt **526**, in diametrically opposite relation to priming ribs **534**. The priming ribs **534** and **536** of each pair are spaced apart by a distance substantially equal to the width of driving recesses **164** and **166**, respectively, of driving body **120**, and fit thereinto when closure cap **520** is positioned and slightly threaded onto adapter **320**. In other words, during the initial threading operation, priming ribs **534** and **536** fall into recesses **164** and **166**.

When closure cap **520** is removed from metered powder dose dispenser **10**, metered dose hole **184** is in alignment with venturi conduit **64**, ready for inhalation by the user. When closure cap **520** is threaded back onto adapter **320**, priming ribs **534** and **536** fall into driving recesses **164** and **166** of driving body **120**. Thus, closing rotation of closure cap **520** causes the same rotation of driving body **120**, and thereby of venturi conduit **64** relative to metered dose hole **184**, to the stored position, 180° out of alignment. As discussed above, during this travel, powder **62** is scraped into metered dose hole **184**, so that metered powder dose dispenser **10** is primed.

When the user is ready to use metered powder dose dispenser **10**, closure cap **520** is unscrewed from adapter **320**. During such movement, priming ribs **534** and **536**, which are engaged with driving recesses **164** and **166** of driving body **120**, cause opposite rotation of driving body **120**, and thereby of venturi conduit **64** relative to metered dose hole **184**, to a position in alignment. Thus, as soon as closure cap **520** is removed, metered dose hole **184**, which is filled with powder **62**, is in alignment with venturi conduit **64**, and ready for inhalation. There is thus no need to provide any additional priming and set-up operation after closure cap **520** is removed. Of course, dispenser **10** could be operated with cap **520** removed by rotating powder housing **20** back and forth relative to adapter **320**.

Further, closure cap **520** includes three equiangularly spaced protrusions **538** formed at the inner surface of covering wall **522**, spaced a small distance from top wall **524**.

To protect powder **62** against moisture contamination, a desiccant holder **560** is held by protrusions **538** within closure cap **520**. As shown in FIGS. **64–66**, desiccant holder **560** includes a circular top wall **562** and an annular side wall **564** extending down from the periphery thereof. An annular recess **566** is formed in the inner surface of annular side wall **564** at the lower end thereof for receiving a disc (not shown)

which holds a desiccant, such as silica gel, therein. An annular rib **568** is formed on the outer surface of annular side wall **564**. In this manner, desiccant holder **560** is inserted within closure cap **520**. Due to the resilience of the plastic pieces, annular rib **568** rides over protrusions **538**, so that desiccant holder **560** is held within closure cap **520** adjacent top wall **524** thereof.

A slight modification to desiccant holder **560** is shown in the assembled view of FIG. **4**, in which an annular groove **570** is formed on the inner surface of annular side wall **564** to hold a disc **572** containing the desiccant.

In accordance with the present invention, a counter mechanism **580** is provided for counting the number of doses that have been dispensed or indicating the number of doses that remain to be dispensed, so as to warn the user of impending powder depletion. Many types of mechanical and electrical counters are useful. A digital electronic counter can be disposed within the base or other areas of the device, and will require electrically conductive contacts which complete a circuit at some point in the dose loading operation; the characteristics of the required battery will be a factor in establishing a shelf life for the device. Presently preferred is counter mechanism **580**, a decrementing mechanical counter that indicates the number of doses remaining to be dispensed.

Counter mechanism **580** is comprised of the aforementioned first and second rotation prevention spring detents **224** and **232** on base **200**, the aforementioned transparent plastic window **330** of adapter **320**, a continuous counter ring **590**, an intermittent counter ring **620** and a spring-biased pawl assembly **640**.

As shown in FIGS. **3**, **4** and **67–70**, continuous counter ring **590** is formed by a disc **592** having a wall with a substantially rectangular cross-section. An outer annular ledge **594** is formed on the outer, upper edge of disc **592** by cutting away disc **592** thereat. Further, a lower annular lip **596** axially extends from the lower, outer edge of disc **592**, as a smooth extension of disc **592**, but of a lesser cross-sectional width. As a result, an inner annular ledge **598** is formed at the lower edge of disc **592**. In this regard, continuous counter ring **590** can be seated on base **200**, and in particular, inner annular ledge **598** seats upon circular top wall **202** of base **200** and lower annular lip **596** seats on annular ledge **206** of base **200** in surrounding relation to circular top wall **202**.

A plurality of numerical indicia **600** are printed on the smooth combined outer surface of disc **592** and lower annular lip **596**. Specifically, two successive sets of numbers "0" through "9" are printed equiangularly thereabout. It will be appreciated, however, that counting indicia other than numerical indicia **600**, can be used, such as color designations, shape designations, Roman numerals, days of the week, and the like.

Twenty gear teeth **602** are equiangularly formed on the inner surface of disc **592** in correspondence with the twenty numbers of numerical indicia **600**. All gear teeth **602** have the same depth in the radial direction, with the exception that diametrically opposite gear teeth **604** and **606** of gear teeth **602**, corresponding to the opposite numbers "1" of numerical indicia **600**, are deeper than the remaining gear teeth **602**, that is, gear teeth **604** and **606** extend outwardly in the radial direction to a greater extent than the remaining gear teeth **602**. When continuous counter ring **590** is seated on base **200**, first rotation prevention spring detent **224** of base **200** engages with one gear tooth **602** at a time, to prevent clockwise rotation of continuous counter ring **590** on base **200**.

As shown in FIGS. **3**, **4** and **71–74**, intermittent counter ring **620** is formed by a disc **622** having a wall with a substantially rectangular cross-section. A lower annular lip **624** axially extends from the lower, outer edge of disc **622**, as a smooth extension of disc **622**, but of a lesser cross-sectional width. As a result, an inner annular ledge **626** is formed at the lower edge of disc **622**. In this regard, intermittent counter ring **620** can be rotatably seated on continuous counter ring **590**, and in particular, inner annular ledge **626** is spaced above continuous counter ring **590**, while lower annular lip **624** seats on outer annular ledge **594** of continuous counter ring **590**.

A plurality of numerical indicia **628** are printed on the smooth combined outer surface of disc **622** and lower annular lip **624**. Specifically, numbers "01" through "20" are printed equiangularly thereabout. Only one such number is shown in FIG. **74**. It will be appreciated, however, that counting indicia other than numerical indicia **628** can be used, such as color designations, shape designations, Roman numerals, days of the week, and the like.

Twenty gear teeth **630** are equiangularly formed on the inner surface of disc **622** in correspondence with the twenty numbers of numerical indicia **628**. All gear teeth **630** have the same depth in the radial direction. When intermittent counter ring **620** is seated on continuous counter ring **590**, second rotation prevention spring detent **232** of base **200** engages with one gear teeth **630** at a time, to prevent clockwise rotation of intermittent counter ring **620** on base **200**. As will be appreciated from the discussion which follows, gear teeth **630** extend along a larger diameter circle than gear teeth **602**, so that gear teeth **630** are outwardly displaced in the radial direction from gear teeth **602**.

Further, a dose limiting tab **632** extends upwardly from the upper surface of disc **622**, corresponding to a position between numbers "01" and "20", to prevent operation of metered powder dose dispenser **10** after a prescribed number of doses have been dispensed. For example, where metered powder dose dispenser **10** is limited to dispensing **200** doses, dose limiting tab **632** will abut against dosage limiter tab **336** of adapter **320** after dispensing of the two hundredth dose, to prevent further relative rotation of powder housing **20** with respect to metering dose plate **180**, as will be described with respect to the operation hereinafter.

Initially, number "20" of indicia **628** is aligned with number "0" of indicia **600** to form the number **200**, which is exposed through transparent plastic window **330** of adapter **320**. After the first dose is dispensed, both continuous counter ring **590** and intermittent counter ring **620** rotate together to expose the numbers "19" and "9", respectively, to form the number "199" which is exposed through window **330**. After the next nine doses, only continuous counter ring **590** rotates one increment at a time for each dose. After the number "190" is exposed through window **330**, the next dose results in both continuous counter ring **590** and intermittent counter ring **620** rotating to form the number "189". This operation continuous until the number "00" is exposed through window **330**. At this time, intermittent counter ring **620** has been rotated to a position so that dose limiting tab **632** abuts against dosage limiter tab **336** of adapter **320**, to prevent further relative rotation of powder housing **20** with respect to metering dose plate **180**.

In order to cause such rotation of continuous counter ring **590** and intermittent counter ring **620**, spring-biased pawl assembly **640** includes a pawl driver **642**, as shown in FIGS. **3**, **4** and **75–79**. Pawl driver **642** includes an arcuate wall **644** having inwardly extending inturned flanges **646** and **648** at opposite side edges thereof. Arcuate wall **644** has a height

greater than the combined height of continuous counter ring **590** and intermittent counter ring **620**. A U-shaped retainer **650** is connected to the free ends of inturned flanges **646** and **648**. U-shaped retainer **650** has a height less than that of arcuate wall **644**. Accordingly, a loop defining an open area **652**, is formed by arcuate wall **644**, flanges **646** and **648** and U-shaped retainer **650**.

A pawl **654** is formed on the outer or convex surface of arcuate wall **644**. Thus, when pawl driver **642** is inserted on circular top wall **202** of base **200** in surrounding relation to cylindrical boss **216**, pawl **654** can be inserted within a gear tooth **602**. However, because gear teeth **630** extend along a larger diameter circle than gear teeth **602**, pawl **654** can only engage with gear teeth **602** and not with gear teeth **630**. The only exception is when pawl **654** engages within one of gear teeth **604** or **606**. In such case, because gear teeth **604** and **606** are deeper than the remaining gear teeth **602**, pawl **654** can reach into and engage with gear teeth **630**. Since gear teeth **604** and **606** are spaced apart by ten gear teeth, pawl **654** engages within one of the gear teeth **604** or **606** every tenth dose dispensing, and thereby engages within one of gear teeth **630** at such time to rotatably drive intermittent counter ring **620** with continuous counter ring **590**.

In order to bias pawl **654** into engagement with gear teeth **602**, two spaced-apart L-shaped holders **656** are formed at the upper end of the concave or inner surface of arcuate wall **644**. A flat spring **658** is bent into a checkmark configuration, with the free end of the larger length portion **660** being frictionally retained within L-shaped holders **656**, while the free end of the short length portion **662** pushes against cylindrical boss **216** of base **220**, thereby biasing pawl assembly **640** outwardly in the radial direction. This causes pawl **654** to enter into engagement with gear teeth **602**.

As an alternative to the combination of pawl assembly **640** and flat spring **658**, the pawl assembly can be fabricated from a somewhat resilient plastic material to have an appendage extending downward at an oblique angle, this appendage acting as a spring to bias the pawl assembly against cylindrical boss **216** as described above.

The operation of counter mechanism **580** will be described with respect to the schematic views of FIGS. **80–82**. Lower spring retainer **260** rotates with reservoir body **22** 180° relative to metering dose plate **180** between the stored position when closure cap **520** is threaded onto adapter **320** and the inhalation position when closure cap **520** is removed from adapter **320**. FIG. **80** shows the relative position between arcuate pawl driving wall **274** of lower spring retainer **260**, continuous counter ring **590**, intermittent counter ring **620** and pawl assembly **640**, when metered powder dose dispenser **10** is in the stored position. In such position, pawl **654** is engaged within a shallow gear tooth **602** of continuous counter ring **590**, and therefore, does not engage with a gear tooth **630**. Further, in such position, pawl driving end **276** of arcuate pawl driving wall **274** engages with pawl assembly **640**.

When reservoir body **22** is rotated the first 178° toward the inhalation position, pawl driving end **278** of arcuate pawl driving wall **274** is rotated into engaged with the opposite side of pawl assembly **640**, as shown in FIG. **81**. As a result, as shown in FIG. **81**, pawl **654** is rotated in the clockwise direction of FIG. **81**, whereby pawl **654** rides out of the shallow gear tooth **602**, thereby compressing spring **658**. Continued rotation to the full 180°, as shown in FIG. **82**, causes pawl **654** to rotate a slight amount and fall into the next gear tooth **604**, which is a deep gear tooth, for example. Specifically, when pawl **654** moves from the position of FIG. **81** to the position of FIG. **82**, spring **658** biases pawl **654** into gear tooth **604**. Since gear tooth **604** is a deep gear tooth, pawl **654** also enters one of the gear teeth **630**. At this point, metered powder dose dispenser **10** is in the inhalation position in which metered dose hole **184** is in alignment with venturi conduit **64**.

After the user inhales the dose of powder **62**, closure cap **520** is threaded back onto adapter **320**. As a result, reservoir body **22** rotates back to its initial position of FIG. **80**, which also results in rotation of lower spring retainer **260**. During this rotation back 180°, that is, in the counterclockwise direction of FIG. **80**, pawl driving end **276** of arcuate pawl driving wall **274** engages with pawl assembly **640** at the end of its movement to rotate pawl assembly **640** in the counterclockwise direction of FIG. **80** to its initial position. During such movement, since pawl **654** is engaged within deep gear tooth **604** and one of the gear teeth **630**, both continuous counter ring **590** and intermittent counter ring **620** are rotated together one increment. In the case where pawl **654** is not engaged with one of the deep gear teeth **604** or **606**, pawl does not engage with a gear tooth **630**, so that only the continuous counter ring **590** would be rotated.

It will be appreciated that continuous counter ring **590** and intermittent counter ring **620** cannot rotate in the clockwise direction of FIGS. **80–82** because of first and second rotation prevention spring detents **224** and **232** which engage with gear teeth **602** and **630**, respectively.

It will be appreciated that various changes can be made to the scope of the present invention. For example, rotation of metering dose plate **180** need not be 180°, but could be for a lesser or greater arcuate distance. In such case, the length of arcuate pawl driving wall **274** would be changed to incrementally drive pawl assembly **640**.

Accordingly, with the present invention, a metered powder dose dispenser **10** is provided that accurately measures the doses of powdered medicament to be delivered to the patient. Specifically, dispenser **10** is greatly simplified in construction and assembly over the prior art.

All of the above elements, with the exception of springs **290** and **658**, are preferably fabricated from readily available plastics, while the springs are preferably fabricated from suitable metals. Typically, the various components which do not require porosity or other special properties will be molded from one or more thermoplastic substances having the desired rigidity and strength. In some embodiments, the component containing the powder receptacle is relatively thin and, to maintain a required degree of surface flatness, will be constructed from a less easily deformed substance such as a reinforced plastic, ceramic or metal. Of course, materials selected must be chemically compatible with the medication to be dispensed. For reasons of cost, a maximum utilization of plastics will be preferred where the device is intended to be disposable with no, or only a limited number of, medicament refills after the initial charge has been dispensed.

A presently preferred embodiment of reservoir plug **90** comprises a thin, circular plate of electropolished stainless steel, which is insert molded onto a plastic base material. The metal portion contacts dosing plate **180** in the assembled device, providing a very flat, smooth and rigid surface to prevent powder leakage from the reservoir. In addition, the metal dissipates any static electricity charges generated by friction between surfaces during dose loading operations, which charges can adversely affect powder flow into and out of the dosing station. Other "composite" components can be used elsewhere in the device where special properties are required.

In order to assemble metered powder dose dispenser **10**, powder housing **20** is first assembled. Specifically, reservoir

plug 90 is inserted within reservoir body 22, flat spring 658 is inserted within L-shaped holders 656 of pawl assembly 640, desiccant holder 560 is snapped into closure cap 520, swirl nozzle 380 is assembled with driving body 120 and mouthpiece 440 is assembled with swirl nozzle 380. Next, continuous counter ring 590 is fit onto base 200 and intermittent counter ring 620 is fit onto continuous counter ring 590. Both counter rings 590 and 620 are rotated until the number "10" of intermittent counter ring 620 and the number "0" of continuous counter ring 590 are in alignment with small slot 214 of base 200. In other words, this corresponds to the number "100", and is directly opposite the number "200" which will be displayed through window 330 of adapter 320.

Pawl assembly 640 with spring 658 therein, is then positioned on top circular wall 202 of base 200 in surrounding relation to cylindrical boss 216, with pawl 654 being biased into engagement with gear tooth 604 in alignment with the number "1" and the gear tooth 630 in alignment with the number "11", that is, in alignment with the number "111". It will be appreciated that first and second rotation prevention spring detents 224 and 232 are in alignment with gear tooth 606 corresponding to number "1" and with the gear tooth 630 corresponding to the opposite number "11".

Thereafter, lower spring retainer 260 is positioned on boss 216 in surrounding relation to retaining post 218, with narrow driven ear 270 in alignment with the number "100" on rings 590 and 620. In such case, pawl driving end 276 thereof is in abutment with inwardly extending inturned flange 648 of pawl assembly 640. Coil spring 290 is then seated on disc 262 of lower spring retainer 260, and support plate 300 is placed on top of coil spring 290, with narrow driven ear 306 thereof in alignment with narrow driven ear 270 of lower spring retainer 260. Then, annular mounting post 188 of metering dose plate 180 is positioned through central circular hole 310 of support plate 300 and over retaining post 218 of base 200, with flats 190 and 222 in alignment. In such case, metered dose hole 184 is in alignment with radially extending slot 312 of support plate 300.

Then, reservoir body 22, having reservoir plug 90 assembled therewith, is inserted over metering dose plate 180, support plate 300, coil spring 290 and lower support plate 260, such that narrow driven ears 270 and 306 fit within narrow drive slot 34, and wider driven ears 272 and 308 fit within wider drive slot 36 of reservoir body 22. In such case, venturi conduit 64 is in alignment with metered dose hole 184. In order to assemble the above parts together, adapter 320 is then placed over the above assembly such that bridge 326 thereof is in alignment with small slot 214 of base 200. Adapter 320 is then pressed down until annular ledge 210 of base 200 snaps into annular groove 324 of adapter 320. At this time, coil spring 290 is compressed, the number "200" appears through window 330 of adapter 320, and recesses 340 and 342 of adapter 320 are in alignment with drive slots 34 and 36, respectively, of reservoir body 22.

Thereafter, powder supply conduit 60 is filled through the upper open end thereof. Then, driving body 120, with nozzle 380 and mouthpiece 440 thereon, is fit over reservoir body 22, such that circular plug conduit 144 of driving body 120 plugs the upper open end of powder supply conduit 60 and such that the upper open end of venturi conduit 64 extends through circular opening 142 in driving body 120. In this position, the lower edge of lower annular skirt section 128 of driving body 120 is positioned immediately above the upper edge of upper annular wall 332 of adapter 320.

Closure cap 520 is then threaded onto adapter 320, whereby powder housing 20 is rotated 180° relative to metering dose plate 180 so as to prime metered powder dose dispenser 10, that is, so as to scrape powder 62 into metered dose hole 184. This moves pawl 654 to the next gear tooth 602, as shown in FIG. 82.

When a user desires to inhale a dosage of the powder 62, closure cap 520 is unthreaded and removed, thereby rotating powder housing 20 back 180° so as to align venturi conduit 64 with metered dose hole 184, ready for inhalation. At this time, pawl 654 is rotated one increment back to the position shown in FIG. 80, whereby the next number "199" is displayed through window 330. When all 200 doses have been used, dose limiting tab 632 of intermittent counter ring 620 abuts against dosage limiter tab 336 of adapter 320 to prevent further rotation for dispensing. Accordingly, the numbers will not continue from "00" to "200".

Referring now to FIGS. 83–105, there is shown an alternative embodiment of a counter mechanism 580' for counting the number of doses that have been dispensed or indicating the number of doses that remain to be dispensed so as to warn the user of impending powder depletion, in which elements corresponding to counter mechanism 580 are identified by the same reference numerals with a prime thereafter. As with counter mechanism 580, it is preferable that counter mechanism 580' is a decrementing counter that indicates the number of doses that remain to be dispensed.

Basically, as part of the counter mechanism 580', the parts that have been modified are base 200', lower spring retainer 260', continuous counter ring 590', intermittent counter ring 620' and spring biased pawl assembly 640'.

In the first place, base 200' includes a circular top wall 202' having an annular skirt 204' extending downwardly from the periphery thereof. The peripheral edge of circular top wall 202' is cut-away to define an outer annular ledge 206'. An annular supporting lip 208' is formed on the outer surface of annular skirt 204' at the lower end thereof, so as to extend outwardly therefrom in the radial direction of annular skirt 204'. In addition, an annular retaining rim 210' is formed on the outer surface of annular skirt 204', parallel to supporting lip 208' and spaced thereabove, so as to extend outwardly from annular skirt 204' in the radial direction thereof. Retaining rim 210' has a diameter less than the diameter of supporting lip 208'. Thus, an annular retaining gap 212' is formed between supporting lip 208' and retaining rim 210'. It will be appreciated that, rather than retaining rim 210' being cut away along a very small arcuate distance to define a small slot therein, as in slot 214 of base 200, a small slot 214' is formed in supporting lip 208' for the same purpose. In addition, retaining rim 210' has a frusto-conical upper annular surface.

A cylindrical boss 216' is formed centrally and axially on the upper surface of circular top wall 202', and a coaxial retaining post 218' of lesser diameter than cylindrical boss 216' is formed at the upper end of cylindrical boss 216'. Accordingly, an outer annular ledge 220' is formed at the upper edge of cylindrical boss 216'. Retaining post 218' has an outer diameter slightly less than the inner diameter of annular mounting post 188 of metering dose plate 180. Retaining post 218' is formed with a slot 222' along the length thereof. In such case, mounting post 188 has a corresponding pin projection (not shown). Accordingly, due to the pin projection and slot 222', mounting post 188 of metering dose plate 180 is retained on retaining post 218' in a non-rotatable manner to ensure that metering dose plate 180 will remain stationary with respect to powder housing 20 when powder housing 20, which includes reservoir body 22, reservoir plug 90 and driving cap 120, is rotated.

As part of the counter mechanism, a first rotation prevention sparing detent 224' is mounted in a cantilever manner on

circular top wall 202'. Specifically, a curved vertical detent supporting wall 226' extends upwardly from circular top wall 202' such that the upper edge of spring detent 224' is substantially coplanar with the upper edge of cylindrical boss 216', and first rotation prevention spring detent 224' extends from one edge 228' of detent supporting wall 226', parallel to and spaced above circular top wall 202'. Further, the free end of first rotation prevention spring detent 224' is provided with a bevel 230' thereat which is oriented in the radial direction of circular top wall 202'.

A second rotation prevention spring detent 232' is mounted in a cantilever manner on circular top wall 202'. Specifically, second rotation prevention spring detent 232' extends from edge 228' of detent supporting wall 226', parallel to and spaced below first rotation prevention spring detent 224' and between first rotation prevention spring detent 224' and circular top wall 202'. The free end of second rotation prevention spring detent 232' is provided with an end 234' thereat having an increased thickness of a particular configuration, as will be explained hereinafter.

A sectored recess 236' is formed in circular top wall 202' in correspondence with detents 224' and 232'. Specifically, recess 236' includes a first radial boundary 238' substantially in line with the free end of detent 232', a second radial boundary 240 substantially in line with the connected end of detent 232', and a third boundary 242' connected between the inner ends of radial boundaries 238' and 240' and extending in alignment with the lengthwise direction of detent 232'.

In addition, a dosage limiting wall 243' is provided on the upper surface of top wall 202', extending from an edge of detent supporting wall 226' radially outwardly to the peripheral edge of top wall 202'. Dosage limiting wall 243' provides the same function as dosage limiter tab 336 of the first embodiment which is formed on the inner surfaces of connecting section 334 and lower annular wall 322. Dosage limiter tab 243' thereby prevents operation of the metered powder dose dispenser after a prescribed number of doses, for example, 200, have been dispensed, as will be understood from the explanation hereinafter.

As shown in FIGS. 88–92, spring retainer 260', which is mounted on annular ledge 220', over retaining post 218', includes a disc 262' having a central opening 264' sized to receive retaining post 218'. An annular boss 266' extends from the lower surface of disc 262' in surrounding relation to central opening 264'. When retaining post 218' extends through annular boss 266' and central opening 264', the lower edge of annular boss 266' seats upon annular ledge 220'.

An upper annular retaining lip 268' extends upwardly from the peripheral edge of disc 262'. Further, two radially extending driven ears 270' and 272' are formed in diametrically opposite positions at the peripheral edge of annular lip 268'. Ear 270' has a width substantially equal to the width of drive slot 34 of reservoir body 22 so as to fit therein and be driven thereby, and ear 272' has a width substantially equal to the width of drive slot 36 of reservoir body 22 so as to fit therein and be driven thereby.

Further, an arcuate pawl driving wall 274' extends from the lower surface of disc 262' between annular boss 266' and the periphery of disc 262'. Opposite ends of arcuate pawl driving wall 274' terminate in radially extending pawl driving end walls 276' and 278', each of which extends radially between annular boss 266' and the respective end of arcuate pawl driving wall 274', although pawl driving end wall 278' extends radially outwardly slightly past the end of arcuate pawl driving wall 274', the reason for which will be explained hereinafter. The arcuate distance between pawl driving end walls 276' and 278' is approximately 190°.

As shown in FIGS. 93–97, continuous counter ring 590' is formed by a disc 592' having a wall with a substantially rectangular cross-section. An outer annular ledge 594' is formed on the outer, lower edge of disc 592' by cutting away disc 592' thereat.

A plurality of numerical indicia 600' are printed on the smooth outer surface of disc 592'. Specifically, two successive sets of numbers "0" through "9" are printed equiangularly thereabout. It will be appreciated, however, that counting indicia other than numerical indicia 600', can be used, such as color designations, shape designations, Roman numerals, days of the week, and the like.

Twenty gear teeth 602' are equiangularly formed on the inner surface of disc 592' in correspondence with the twenty numbers of numerical indicia 600'. All gear teeth 602' have the same depth in the radial direction, with the exception that diametrically opposite gear teeth 604' and 606' of gear teeth 602', corresponding to a position between numbers "4" and "5" of numerical indicia 600', are deeper than the remaining gear teeth 602', that is, gear teeth 604' and 606' extend outwardly in the radial direction to a greater extent than the remaining gear teeth 602'. When continuous counter ring 590' is correctly positioned in the apparatus as will be explained hereinafter, first rotation prevention spring detent 224' of base 200' engages with one gear tooth 602' at a time, to prevent clockwise rotation of continuous counter ring 590' on base 200'.

As shown in FIGS. 98–101, intermittent counter ring 620' is formed by a disc 622' having a wall with a substantially rectangular cross-section.

A plurality of numerical indicia 628' are printed on the smooth outer surface of disc 622'. Specifically, numbers "0" through "20" are printed equiangularly thereabout. Only a few such numbers are shown in FIG. 101. It will be appreciated, however, that counting indicia other than numerical indicia 628' can be used, such as color designations, shape designations, Roman numerals, days of the week, and the like, may be used.

An inner annular wall 629' is provided on the inner surface of disc 622' at a position approximately two-thirds of the height of disc 622', as shown in FIG. 100. Twenty gear teeth 630' are equiangularly formed on the inner surface of inner annular wall 629' in correspondence with the twenty numbers of numerical indicia 628'. All gear teeth 630' have the same depth in the radial direction. It will be appreciated that each tooth 630' has an outer, substantially circumferentially extending portion 631' and a sloped portion 633' extending inwardly from outer, substantially circumferentially extending portion 631'. Because of circumferentially extending portion 631', the circumferential length of the sloped portion 633' is reduced and thereby made steeper than in the first embodiment of gear teeth 630. In this regard, free end 234' of second rotation prevention spring detent 232' of base 200', which has an increased thickness, has a configuration corresponding to that of gear teeth 630'. As a result of the circumferentially extending portion 631' and the increased slope of sloped portion 633', there is a greater torque that is necessary to move intermittent counter ring 620'. The reason for this arrangement is to prevent undesirable movement of intermittent counter ring 620' due to frictional forces with continuous counter ring 590', when it is desired that only continuous counter ring 590' should rotate.

With this arrangement, intermittent counter ring 620' is seated on base 200', and in particular, the lower edge of disc

622' seats upon annular ledge 206' of base 200' in surrounding relation to circular top wall 202'. When intermittent counter ring 620' is so seated, second rotation prevention spring detent 232' of base 200' engages with one gear tooth 630' at a time, to prevent clockwise rotation of intermittent counter ring 620' on base 200'. As will be appreciated from the discussion which follows, gear teeth 630' extend along a larger diameter circle than gear teeth 602', so that gear teeth 630' are outwardly displaced in the radial direction from gear teeth 602'.

Further, continuous counter ring 590' is rotatably seated on intermittent counter ring 620', and in particular, outer annular ledge 594' seats on the upper edge of disc 622' for rotation relative thereto. It will be appreciated that this is the reverse of the first-mentioned embodiment in which intermittent counter ring 620 sits on continuous counter ring 590.

Further, a dose limiting tab 632' extends downwardly from the lower surface of inner annular wall 629', corresponding to a position at the number "05", to prevent operation of metered powder dose dispenser 10 after a prescribed number of doses have been dispensed. For example, where metered powder dose dispenser 10 is limited to dispensing 200 doses, dose limiting tab 632' will abut against dosage limiting wall 243' of base 200', after dispensing of the two hundredth dose, to prevent further relative rotation of powder housing 20 with respect to metering dose plate 180.

Initially, number "20" of indicia 628' is aligned with number "0" of indicia 600' to form the number "200", which is exposed through transparent plastic window 330 of adapter 320. After the first dose is dispensed, both continuous counter ring 590' and intermittent counter ring 620' rotate together to expose the numbers "19" and "9", respectively, to form the number "199" which is exposed through window 330. After the next nine doses, only continuous counter ring 590' rotates one increment at a time for each dose. After the number "190" is exposed through window 330, the next dose results in both continuous counter ring 590' and intermittent counter ring 620' rotating to form the number "189". This operation continues until the number "00" is exposed through window 330. At this time, intermittent counter ring 620' has been rotated to a position so that dose limiting tab 632' abuts against dosage limiting wall 243' of base 200', to prevent further relative rotation of powder housing 20 with respect to metering dose plate 180.

In order to cause such rotation of continuous counter ring 590' and intermittent counter ring 620', spring-biased pawl assembly 640' includes a pawl 654' having a substantially triangular configuration, secured near one end of a flat, plastic spiral spring 658', as shown in FIGS. 102–104. Pawl 654' has a height equal to the height of spring 658'. In addition, a pawl extension 655' of the same configuration as pawl 654' is mounted on top of pawl 654' so as to extend above spring 658'. Pawl extension 655' has a long radial face 657' and a substantially parallel short radial face 659', with short radial face 659' terminating in an angled face 661' that is connected to the end of long radial face 657'.

As an alternative, as shown in FIG. 105, an S-shaped spring 658" can be used in place of spiral spring 658'. In FIG. 105, spring detents 224' and 232' have been omitted for the sake of clarity.

When pawl assembly 640' is inserted on circular top wall 202' of base 200' in surrounding relation to cylindrical boss 216', pawl extension 655' is biased by spring 658' within a gear tooth 602'. However, because gear teeth 630' extend along a larger diameter circle than gear teeth 602', pawl 654' does not engage with gear teeth 630' at this time. The only exception is when pawl extension 655' engages within one of gear teeth 604' or 606'. In such case, because gear teeth 604' and 606' are deeper than the remaining gear teeth 602', pawl 654' can reach into and engage with gear teeth 630'. Since gear teeth 604' and 606' are spaced apart by ten gear teeth, pawl extension 655' engages within one of the gear teeth 604' or 606' every tenth dose dispensing, and thereby pawl 654' engages within one of gear teeth 630' at such time to rotatably drive intermittent counter ring 620' with continuous counter ring 590'.

The operation of counter mechanism 580' will now be described. Lower spring retainer 260' rotates with reservoir body 22 relative to metering dose plate 180 between the stored position when closure cap 520 is threaded onto adapter 320 and the inhalation position when closure cap 520 is removed from adapter 320.

In the initial position, the number "20" of intermittent counter ring 620' and the number "0" of continuous counter ring 590' are positioned at transparent plastic window 330, so as to display a combined number "200" corresponding to the number of doses remaining. Window 330 is positioned diametrically opposite small slot 214' on base 200'. Also, pawl extension 655' is positioned 90° counterclockwise from slot 214', so that pawl extension 655' is engaged within a deep gear tooth 604' and pawl 654' is engaged within a gear tooth 630'. Further, pawl driving end wall 278' abuts against long radial face 657'. In this position, driven ear 270' is substantially in line with slot 214'.

When reservoir body 22 is rotated from the closed to the open operative position, pawl driving end wall 276' of lower spring retainer 260' is rotated into engagement with short radial face 659' of pawl extension 655'. In this position, driven ear 272' is substantially in line with slot 214'. As a result, pawl 654' and pawl extension 655' are rotated in the counterclockwise direction. During such movement, since pawl extension 655' and pawl 654' are engaged within deep gear tooth 604' and one of the gear teeth 630', respectively, both continuous counter ring 590' and intermittent counter ring 620' are rotated together one increment. Accordingly, the number "19" of intermittent counter ring 620' and the number "9" of continuous counter ring 590' are positioned at transparent plastic window 330, so as to display a combined number "199" corresponding to the number of doses remaining. At this point, metered powder dose dispenser 10 is in the inhalation position in which metered dose hole 184 is in alignment with venturi conduit 64.

After the user inhales the dose of powder 62, closure cap 520 is threaded back onto adapter 320. As a result, reservoir body 22 rotates back to its initial position, which also results in rotation of lower spring retainer 260' in the clockwise direction. During this rotation back, pawl driving end wall 278' of lower spring retainer 260' is rotated into engagement with long radial face 657' of pawl extension 655'. As a result, pawl 654' and pawl extension 655' are rotated in the counterclockwise direction, during which time, pawl extension 655' rides out of the gear tooth 604' and pawl 654' rides out of the gear tooth 630', thereby compressing spring 658'. Continued rotation causes pawl extension 655' to rotate a slight amount and fall into the next gear tooth 602', which is a shallow gear tooth, for example. Specifically, spring 658' biases pawl extension 655' into a shallow gear tooth 602'. Since gear tooth 602' is a shallow gear tooth, pawl 654' does not enter one of the gear teeth 630'. At this position, pawl driving end wall 278' abuts against long radial face 659' and driven ear 270' is substantially in line with slot 214'.

It will be appreciated that during the movement of pawl extension 654' from one gear tooth 602' to another gear tooth

602', pawl extension 654' rides against pawl driving end wall 278'. The reason that pawl driving end wall 278' extends radially outward past arcuate pawl driving wall 274' is to prevent pawl 654' from moving past pawl driving end wall 278' into alignment with arcuate pawl driving wall 274', since this would otherwise prevent compression of spring 658' and thereby prevent pawl extension 655' from moving from one tooth 602' to another tooth 602'.

This operation is continued for each dose. In the case where pawl extension 655' is not engaged with one of the deep gear teeth 604' or 606', pawl 654' does not engage with a gear tooth 630', so that only the continuous counter ring 590' would be rotated.

It will be appreciated that continuous counter ring 590' and intermittent counter ring 620' cannot rotate in the clockwise direction because of first and second rotation prevention spring detents 224' and 232' which engage with gear teeth 602' and 630', respectively.

Accordingly, with the present invention, a counter mechanism is provided which has a high counting capability of doses dispensed or remaining to be dispensed. Specifically, there are two separately rotatable counter rings, one for the ones digits of a counted number and the other for tens and hundreds digits for the counted number, with the counter rings being rotatable along the same common axis as the powder housing.

Further, a swirl nozzle is provided in which there is improved micronization of the powder and improved mixing of the micronized powder with suction air. Specifically, the powder first changes direction from an axial direction of the inhalation or venturi conduit to a transverse direction substantially perpendicular to the axial direction; continuously changes direction in a spiral manner in a swirl cavity extending in the transverse direction; and upon exiting the swirl cavity, changes direction back to the axial direction through a supply chimney, while retaining a swirl component of the flow.

Still further, with the present invention, the metered powder dose dispenser is automatically primed every time that the closure cap is threaded thereon and is automatically ready to use every time that the closure cap is threadedly removed. If multiple actuations are desired for the dose at a given time, the user is not required to repeatedly remove and replace the cap, but can simply perform the reciprocal rotation of either the upper or lower portions of the device while holding the other portion stationary, then replace the cap for storage until the next prescribed dose is due.

Having described specific preferred embodiments of the invention with reference to the accompanying drawings, it will be appreciated that the present invention is not limited to those precise embodiments and that various changes and modifications can be effected therein by one of ordinary skill in the art without departing from the scope or spirit of the invention as defined by the appended claims.

What is claimed is:

1. A powder inhaler comprising:

powder housing means for holding a supply of powdered material to be dispensed, said powder housing means including an inhalation conduit extending therethrough in a first direction, in displaced relation to said supply of powdered material;

metering plate means for holding a metered amount of said powdered material, said metering plate means including metered dose hole means for holding said metered amount of said powdered material, said metering plate means being positionable below said supply of powdered material, and said metering plate means and said powder housing means being relatively bi-directionally rotatable with respect to each other about a common central axis so that said metered dose hole means can be placed in fluid communication selectively with said supply of powdered material or said inhalation conduit;

spring means for biasing said metering plate means and said powder housing means toward each other to maintain contact therebetween;

rotation limiting means for restricting relative rotation between said powder housing means and said metering plate means to a predetermined angle;

counter means for providing a visual count of the number of doses of said powdered material that have been dispensed or remain to be dispensed in response to said relative rotation of said powder housing means and said metering plate means, said counter means including:

counter ring means for providing said visual count, said counter ring means being rotatable about said common central axis and having counting indicia thereon for displaying said visual count, and

actuating means for incrementally rotating said counter ring means in response to said relative rotation between said metering plate means and said powder housing means; and

display means through which one of said counting indicia from said counter ring means is displayed to indicate a count corresponding to a number of doses of powdered material that have been dispensed or remain to be dispensed.

2. The powder inhaler according to claim 1, further including an upper support plate positioned below and in contact with said metering plate means, said upper support plate having an opening larger than said metered dose hole means and in alignment with said metered dose hole means when said metered dose hole means is in alignment with said inhalation conduit, and said retainer means including a material secured to an underside of said upper support plate and formed by a material selected from the group consisting of a gas-permeable filter, a mesh screen, a porous material mesh and a perforated plate element.

3. The powder inhaler according to claim 1, wherein said powder inhaler includes a base having an axially extending retaining post thereon coaxial with said common axis, and said counter ring means is rotatably mounted on said base in surrounding relation to said retaining post.

4. The powder inhaler according to claim 3, wherein said counter ring means includes a continuous counter ring having counting indicia thereon, and an intermittent counter ring coaxially mounted with said continuous counter ring and having counting indicia thereon.

5. The powder inhaler according to claim 4, wherein said continuous counter ring has gear teeth therearound, said intermittent counter ring has gear teeth therearound, and said actuating means includes pawl means engaging with said gear teeth of said continuous counter ring and said intermittent counter ring for rotating said continuous counter ring one increment each time that a dose of the powdered material is dispensed to display another one of said counting indicia of said continuous counter ring through said display means, and for rotating said intermittent counter ring one increment every predetermined number of rotational increments of said continuous counter ring to display another one of said counting indicia of said intermittent counter ring through said display means.

6. The powder inhaler according to claim 5, further including spring means for biasing said pawl means into

engagement with said gear teeth of said continuous counter ring and said intermittent counter ring.

7. A powder inhaler comprising:

powder housing means for holding a supply of powdered material to be dispensed, said powder housing means including an inhalation conduit extending therethrough in a first direction, in displaced relation to said supply of powdered material;

metering plate means for holding a metered amount of said powdered material, said metering plate means including metered dose hole means for holding said metered amount of said powdered material, said metering plate means being positionable below said supply of powdered material, and said metering plate means and said powder housing means being relatively bi-directionally rotatable with respect to each other about a common central axis so that said metered dose hole means can be placed in fluid communication selectively with said supply of powdered material or said inhalation conduit;

spring means for biasing said metering plate means and said powder housing means toward each other to maintain contact therebetween;

a base having an axially extending retaining post thereon coaxial with said central axis;

rotation limiting means for restricting relative rotation between said powder housing means and said metering plate means to a predetermined angle;

counter means for providing a visual count of the number of doses of said powdered material that have been dispensed or remain to be dispensed in response to said relative restricted rotation of said powder housing means and said metering plate means, said counter means including:

counter ring means for providing said visual count and including a continuous counter ring and a coaxially mounted intermittent counter ring, said counter ring means being mounted on said base in surrounding relation to said retaining post, being rotatable about said common central axis and having counting indicia thereon for displaying said visual count, and

actuating means for incrementally rotating said counter ring means in response to said relative rotation between said metering plate means and said powder housing means, said actuating means including gear teeth around each of said continuous counter ring and said intermittent counter ring, and pawl means including a pawl for engagement with gear teeth of one of said counter rings and a pawl extension for engagement with gear teeth of the other of said counter rings, for rotating said continuous counter ring one increment each time that a dose of said powdered material is dispensed and for rotating said intermittent counter ring one increment every predetermined number of rotational increments of said continuous counter ring;

spring means for biasing said pawl means into engagement with said gear teeth, said spring means having said pawl extension secured to the end thereof, at a height above said pawl; and

display means through which at least one of said counting indicia is displayed to indicate a count corresponding to a number of doses of powdered material that have been dispensed or remain to be dispensed.

8. The powder inhaler according to claim 5, wherein said gear teeth of said continuous counter ring are arranged in correspondence with said counting indicia thereon, and said gear teeth of said intermittent counter ring are arranged in correspondence with Said counting indicia thereon.

9. The powder inhaler according to claim 5, wherein the gear teeth of said continuous counter ring include a plurality of successive first gear teeth of a first depth and at least one second gear tooth of a second, greater depth, each said second gear tooth being positioned after every predetermined number of said first gear teeth; and said intermittent counter ring includes a plurality of successive third gear teeth of a depth equal to the depth of each said second gear tooth of said continuous counter ring so that said pawl means engages with successive ones of said first gear teeth during successive dosing operations and engages with one said second gear tooth and a third gear tooth of said intermittent counter ring after a plurality of the dosing operations.

10. The powder inhaler according to claim 9, wherein said first and second gear teeth are formed on an inner surface of said continuous counter ring and said third gear teeth are formed on an inner surface of said intermittent counter ring.

11. The powder inhaler according to claim 5, wherein said pawl-means engages said gear teeth of said continuous counter ring and said intermittent counter ring to rotate said continuous counter ring and said intermittent counter ring in a first rotational direction, and further including detent means for preventing rotation of said continuous counter ring and said intermittent counter ring in a second rotational direction opposite to said first rotational direction.

12. The powder inhaler according to claim 11, wherein said detent means includes first rotation prevention detent means mounted on said base for engaging with one of said first and second gear teeth to prevent rotation of said continuous counter ring in said second rotational direction and second rotation prevention detent means mounted on said base for engaging with one of said third gear teeth to prevent rotation of said intermittent counter ring in said second rotational direction.

13. The powder inhaler according to claim 5, wherein said actuating means further includes pawl driver means for incrementally rotating said pawl means, said pawl driver means including a retainer rotatably mounted on said base coaxially with said continuous counter ring and said intermittent counter ring, said retainer including first pawl driver means for engaging with one side of said pawl means to incrementally rotate said pawl means in a first rotational direction at the end of rotation of said retainer in said first rotational direction and second pawl driver means for engaging an opposite side of said pawl means to incrementally rotate said pawl means in a second, opposite rotational direction at the end of rotation of said retainer in said second, opposite rotational direction.

14. The powder inhaler according to claim 13, wherein said first and second pawl driver means are formed as opposite edges of an arcuate pawl driving wall connected with said retainer.

15. The powder inhaler according to claim 13, wherein said first and second pawl driver means are formed as radially extending pawl driving end walls connected with said retainer.

16. The powder inhaler according to claim 13, wherein said first and second pawl driver means are spaced apart by a distance such that rotation of said retainer by a first arcuate distance causes incremental rotation of said pawl means by a second smaller arcuate distance.

17. The powder inhaler according to claim 13, wherein said powder housing means includes holding means for carrying said retainer with said powder housing means

during said relative rotation between said metering plate means and said powder housing means about said common central axis.

18. The powder inhaler according to claim 17, wherein said holding means includes at least one drive slot in one of said powder housing means and said retainer, and at least one drive ear in the other of said powder housing means and said retainer, said at least one drive ear engaging within said at least one drive slot.

19. The powder inhaler according to claim 5, wherein the gear teeth of said intermittent counter ring have a configuration with an outer, substantially circumferentially extending portion and a sloped portion extending inwardly from said circumferentially extending portion.

20. The powder inhaler according to claim 4, wherein said continuous counter ring is rotatably mounted on said base, and said intermittent counter ring is rotatably mounted on said continuous counter ring coaxially with said continuous counter ring.

21. The powder inhaler according to claim 4, wherein said intermittent counter ring is rotatably mounted on said base, and said continuous counter ring is rotatably mounted on said intermittent counter ring coaxially with said intermittent counter ring.

22. The powder inhaler according to claim 1, further comprising:

nozzle means for breaking up agglomerates of powdered material from said inhalation conduit to form micronized powdered material and for mixing said micronized powdered material with suction air, said nozzle means including either:

(a) cavity means for changing the direction of flow of said powder from said first direction of said inhalation conduit to a second direction different from said first direction, and swirl means for substantially continuously changing the direction of flow of said powder in said second direction in said cavity means; or

(b) an outer wall defining a conduit having a shape substantially of an inverted tornado.

23. The powder inhaler according to claim 22, further including lock-out means for preventing said relative rotation of said powder housing means and said metering plate means after a predetermined number of doses have been dispensed.

24. The powder inhaler according to claim 23, further including a base on which said metering plate means is non-rotatably mounted and an adapter non-rotatably mounted on said base, said lock-out means including a dosage limiter tab on said adapter, and tab means on said counter means for engaging with said dosage limiter tab when said predetermined number of doses have been dispensed.

25. The powder inhaler according to claim 1, further comprising closure cap means for covering said powder housing means and for priming said powder inhaler for use, said closure cap means including priming means for rotating said powder housing means such that said inhalation conduit is in communication with said metered dose hole means when said closure cap means is removed from covering relation of said powder housing means and for rotating said powder housing means such that said inhalation conduit is out of communication with said metered dose hole means and such that said powder supply opening comes into communication with said metered dose hole means when said closure cap means is secured in covering relation to said powder housing means.

26. The powder inhaler according to claim 25, further including adapter means rotatably mounted with respect to said powder housing means and non-rotatably mounted with respect to said metering plate means, said adapter means including first helical threads and said closure cap means including second helical threads for engaging with said first helical threads to threadedly connect said closure cap means on said adapter means.

27. The powder inhaler according to claim 26, wherein said powder housing means includes at least one driving recess and said priming means includes rib means on an inside surface of said closure cap means for engaging with said at least one driving recess to rotate said powder housing means such that said inhalation conduit is in communication with said metered dose hole means when said closure cap means is threadedly removed from said covering relation of said powder housing means and for rotating said powder housing means such that said inhalation conduit is out of communication with said metered dose hole means and such that said powder supply opening comes into communication with said metered dose hole means when said closure cap means is threadedly secured to said adapter means in covering relation to said powder housing means.

* * * * *

Exhibits

Return To
USPTO Home Page
Finance Online Shopping Page

United States Patent and Trademark Office

Patent Bibliographic Data					05/26/2005 06:07 PM
Patent Number:	5829434		**Application Number:**	08446804	
Issue Date:	11/03/1998		**Filing Date:**	06/01/1995	
Title:	INHALER FOR POWDERED MEDICATIONS				
Status:	8th year fee window opens: 11/03/2005			**Entity:**	Large
Window Opens:	11/03/2005	**Surcharge Date:**	05/04/2006	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:	1552	MAINTENANCE FEE DUE AT 7.5 YEARS.			
Surcharge Fee Code:					
Most recent events (up to 7):	2002/05/24 2002/05/21 2002/04/29	Payor Number Assigned. Maintenance Fee Reminder Mailed. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	MASTER DATA CENTER, INC. 29100 NORTHWESTERN HIGHWAY SUITE 300 SOUTHFIELD, MI 480341095				

Run Another Query

Need Help? | USPTO Home Page | Finance Online Shopping Page

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 124

MASTER DATA CENTER, INC.
29100 NORTHWESTERN HIGHWAY
SUITE 300
SOUTHFIELD MI 48034-1095

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,829,434	**$880.00**	**$0.00**	**08/446,804**	**11/03/98**	**06/01/95**	**04**	**NO**	**PAID**	**PD0340K**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Return To

USPTO Home Page

Finance Online Shopping Page

United States Patent and Trademark Office

Maintenance Fees Window Dates 05/26/2005 09:27 PM EDT

Patent Number: 5829434 **Application Number:** 08446804

	4th Year	8th Year	12th Year
Open Date	11/05/2001	11/03/2005	11/03/2009
Surcharge Date	05/06/2002	05/04/2006	05/04/2010
Close Date	11/04/2002	11/03/2006	11/03/2010

Need Help? | USPTO Home Page | Finance Online Shopping Page

Exhibit 6

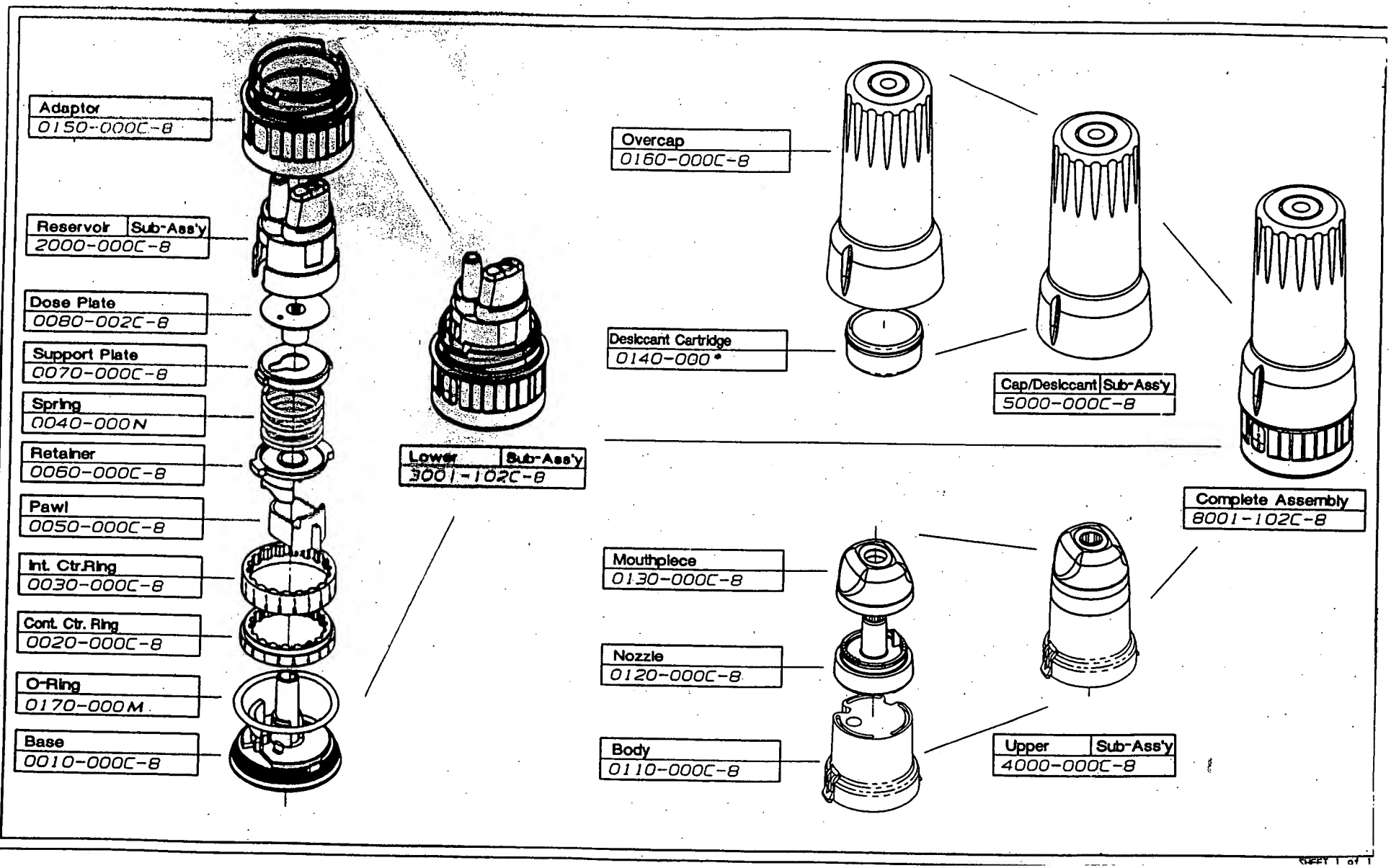

Adaptor
0150-000C-8
Reservoir Sub-Ass'y
2000-000C-8
Dose Plate
0080-002C-8
Support Plate
0070-000C-8
Spring
0040-000N
Retainer
0060-000C-8
Pawl
0050-000C-8
Int. Ctr.Ring
0030-000C-8
Cont. Ctr. Ring
0020-000C-8
O-Ring
0170-000M
Base
0010-000C-8
Lower Sub-Ass'y
3001-102C-8
Overcap
0160-000C-8
Desiccant Cartridge
0140-000*
Cap/Desiccant Sub-Ass'y
5000-000C-8
Complete Assembly
8001-102C-8
Mouthpiece
0130-000C-8
Nozzle
0120-000C-8
Body
0110-000C-8
Upper Sub-Ass'y
4000-000C-8

Exhibit 7

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

September 13, 1994

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

SCH 32088
Mometasone Furoate
Dry Powder Inhaler
Serial No. 000

SUBJECT: INITIAL INVESTIGATIONAL NEW DRUG APPLICATION

Dear Dr. Burke:

We are submitting, in triplicate, an Investigational New Drug Application for Mometasone Furoate (SCH 32088) Dry Powder Inhaler.

We currently have two active INDs for mometasone furoate: IND 32,503 for an oral metered dose inhaler for the treatment of asthma and IND 35,932 for an aqueous nasal spray for the treatment of allergic rhinitis. Mometasone furoate is also the subject of several approved NDAs for dermal use.

This IND is intended to evaluate the use of a mometasone furoate dry powder inhaler (DPI) in the treatment of asthma. Currently, mometasone furoate is being studied in the treatment of asthma (IND 32,503), delivered in an aerosol metered-dose inhaler which contains chloroflurocarbon (CFC). We are developing a powder formulation as an alternative to the use of CFCs. We will begin the clinical development of this formulation under this IND, with a multiple-dose study to evaluate the safety and tolerance of three doses of mometasone furoate powder delivered via a breath activated DPI, administered once daily for 28 days, compared with placebo. Doses of 200 mcg, 400 mcg and 600 mcg will be evaluated in volunteers with moderate asthma.

Previous human experience with the dry powder formulation consists of two clinical pharmacology studies in which 36 healthy adult males were treated (16 of these subjects received mometasone furoate by inhalation as a dry powder inhaler). The single rising dose comparative systemic bioactivity study used doses of 400, 800, 1600 and 3200 mcg of mometasone furoate (this study was conducted overseas). The AME study investigated the absorption of ^{3}H-SCH 32088 (1 mg) powder. The results of these studies are provided in this IND.

Additional supportive safety and efficacy data for mometasone furoate drug substance are provided in this IND through a 395 patient phase II dose ranging study in which mometasone was administered to 237 patients by a metered dose inhaler at doses of 112,

400 and 1000 mcg daily, dosed twice a day for 28 days.

Provided with this IND is a Preclinical Data Handbook requested by Dr. Mukherjee of the Pilot Drug Evaluation Staff in his 11/6/93 fax and 12/20/93 telephone call. He requested this summary volume, in addition to the IND, to provide data summaries of all toxicology (pharmacology and pre-clinical safety) studies with mometasone furoate. Data provided in other INDs are summarized in this volume, with full reports cross-referenced. All study findings whether drug-related or not are reported as requested by Dr. Mukherjee. This summary volume which also contains brief clinical, and chemistry summaries in addition to the pharmacology and pre-clinical summary will be helpful to orient the new reviewers to our overall mometasone furoate program.

Subsequent to the submission of the previous IND's for the oral metered dose inhaler and the aqeuous nasal spray, additional preclinical safety studies have been conducted in mice, rats and dogs to evaluate the toxicologic profile of inhaled mometasone furoate. An acute (single dose) inhalation study was conducted in dogs, and two-week and three-month (multiple dose) studies were conducted in both rats and dogs. One- and three-month studies with the aerosol formulation (MDI) were conducted in mice and rats. A three-month study of orally administered mometasone furoate was conducted in dogs. The results of these studies are included in this IND. Additional studies performed by the inhalation, intranasal, oral and intravenous route support this IND and the results are summarized in the preclinical section. These studies were previously submitted to other INDs and are cross-referenced.

We also had a chemistry, manufacturing and controls pre-IND meeting on 7/22/93 with Pilot Drug Chemist, Ms. Yaciw in which we reviewed the technical aspects of the dry powder inhaler. Minutes from that meeting were submitted to IND 35,932 (Serial No. 034) on 8/6/93.

With submission of this IND, we are requesting a meeting to discuss the overall toxicology program for mometasone furoate. We had requested a pre-IND meeting on 6/9/94 and submitted a pre-meeting package on 6/23/94. As indicated by Ms. Cathie Schumaker of your division, a toxicology meeting would be more appropriately scheduled after submission of this IND. We will contact you shortly to schedule this meeting.

Please be advised that the material and data contained in this submission are considered confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j), as well as the FDA regulations.

Sincerely,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

PR:ljg/Enc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1992.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1 NAME OF SPONSOR
Schering Corporation

2. DATE OF SUBMISSION
September 13, 1994

3 ADDRESS *(Number, Street, City, State and Zip Code)*
2000 Galloping Hill Road
Kenilworth, NJ 07033

4 TELEPHONE NUMBER *(Include Area Code)*
(908) 298-2780

5. NAME(S) OF DRUG *(Include all available names Trade, Generic, Chemical, Code)*
Mometasone Furoate (SCH 32088) Dry Powder Inhaler (DPI)

6. IND NUMBER *(If previously assigned)*
TBD

7. INDICATION(S) *(Covered by this submission)*
Asthma

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED. ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9 LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314 420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION

IND 32,503	DMF 5289	DMF 10034	DMF 1500	DMF 5821
IND 35,932	DMF 4164	DMF 7092	DMF 2750	
	DMF 4343	DMF 6676	DMF 3647	

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER: 0 0 0

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☑ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT.

FORM FDA 1571 (6.92) PREVIOUS EDITION IS OBSOLETE

12 **CONTENTS OF APPLICATION**

This application contains the following items: *(check all that apply)*

- ☑ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ☑ 2.Table of contents *[21 CFR 312.23 (a) (2)]*
- ☑ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ☑ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ☑ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☑ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☑ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☑ c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☑ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ☑ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ☑ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ☑ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ☑ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☑ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☑ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☑ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED

14 NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Keith Nolop, M.D.
Director
Clinical Research

Barbara Mesarina-Wicki, M.D.
Associate Director
Clinical Research

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Robert J. Spiegel, M.D.
Senior Vice President
Worldwide Clinical Research

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16 NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Richard N. Spivey, Pharm.D., Ph.D.
Sr. Director, Worldwide Reg. Affairs

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Richard N. Spivey

/[redacted] Dr. Spivey

18 ADDRESS *(Number, Street, City, State and Zip Code)*

2000 Galloping Hill Road
Kenilworth, NJ 07033

19 TELEPHONE NUMBER *(Include Area Code)*

(908) 298-2780

20 DATE

9/13/94

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Exhibit 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 46,216

Date SEP 16 1994

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attn: Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 46,216

Sponsor: Schering Corporation

Name of Drug: Mometasone Furoate (SCH 32008)
Dry Powder Inhaler (DPI)

Date of Submission: September 13, 1994

Date of Receipt: September 14, 1994

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

SEP 1994

Richard N. Spivey, Pharm.D.

FORM FDA 3228a (9/89) PREVIOUS EDITION IS OBSOLETE.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-150)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact

Sincerely yours,

Sandy Barnes for

Supervisory Consumer Safety Officer
Division of Oncology and Pulmonary
Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-150 - yellow
HFD-150/CSO - green

IND ACKNOWLEDGEMENT

Exhibit 9

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

November 30, 1998

John Jenkins, M.D., Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
HFD-570, Room 10B03
5600 Fishers Lane
Rockville, MD 20857

NDA 21-067
TRADEMARK 220 mcg/430 mcg
(mometasone furoate
inhalation powder)

SUBJECT: ORIGINAL NEW DRUG APPLICATION

Dear Dr. Jenkins:

This is an original New Drug Application for a mometasone furoate inhalation powder product for the treatment of asthma. Mometasone furoate (MF) is a glucocorticoid with proven anti-inflammatory activity, currently marketed in the United States and internationally as the active component of Nasonex (mometasone furoate monohydrate) Nasal Spray 50 mcg for the treatment of seasonal and perennial allergic rhinitis, and Elocon, Elocom, Elomet, or Ecural products for dermatologic use.

The MF inhalation powder product incorporates an assembled plastic dosing mechanism which contains the drug agglomerate storage reservoir and inhalation mouthpiece. Two marketed strengths are planned: 220 mcg or 430 mcg MF per metered dose, delivering 200 mcg or 400 mcg respectively from the mouthpiece.

Doses described throughout this application generally refer to doses delivered from the mouthpiece rather than metered doses unless otherwise specified.

Within component documents, the product may alternately be referred to as mometasone furoate dry powder inhaler (MF DPI), MF DPI (lactose formulation), or MF lactose-mix DPI. Mometasone furoate may also be referred to as SCH 32088.

This application includes clinical efficacy and safety data from nine multicenter trials involving over 3500 patients with varying degrees of asthma severity treated with MF or comparators for up to 12 weeks. The clinical content and format of this application were discussed with the Division of Pulmonary Drug Products at the April 4, 1998 End of Phase 2 Teleconference and the September 14, 1998 preNDA meeting. As agreed per the preNDA meeting, long-term safety data involving over 200 patients treated with MF for one year will be provided in a planned safety update to be provided no later than 4 months post initial NDA submission.

Also per the above-referenced discussions, it was agreed that Biopharmaceutics studies required for this application would be limited in accordance with the degree of systemic availability observed following inhalation of the largest single recommended dose of the product for non-oral steroid dependent patients.

Chemistry, Manufacturing and Controls issues for this product were discussed with the Division in the meetings of February 10, 1997, April 27, 1998 and September 14, 1998.

Applicable preclinical information with respect to the pharmacology of MF has been substantially described in previously reviewed New Drug Applications as referenced within this document. As agreed with the Division of Pulmonary Drug Products in meetings of May 17, 1995 and August 16, 1995, preclinical studies which bridge the previous MF information to the current dose form are included in this application. Pharmacology/Toxicology format and content were additionally discussed in the End of Phase 2 and preNDA conferences referenced above. As requested, animal line listings for several studies have been provided in SAS Transport Version 5 format for several studies. These files are contained on nine Compact Discs (CD-ROMs) included with the Review Copy only.

This submission is being provided in hardcopy and electronic format. We have followed the draft guidance "Providing Regulatory Submissions in Electronic Format - NDA's" issued in April of this year. The electronic portion of the submission is divided into two sections. The first section contains read only files consisting of reports, summaries, etc., and is presented in portable document format (pdf). The second section consists of the data portion, presented in SAS Transport file format. Labeling and selected summary documents and reports are additionally provided in Microsoft Word as requested.

When copying the CD-ROM contents to your file server, be aware that Item 8 (Clinstat) and Item 12 (CRF) are distributed onto multiple CD-ROMs. The contents of the "Clinstat" directory on CD 3 of 7 should be copied into the "Clinstat" directory previously created when the contents of CD 2 was copied to your file server. The contents of the "CRF" directory on CDs 5 through 7 should be copied into the "CRF" directory previously created when the contents of CD 4 was copied to your file server. This will ensure the integrity of the submission directory structure.

A check in the amount of $256,338 was sent to FDA's designated Pittsburgh location on November 20, 1998. This check represented the estimated user fee amount for the current fiscal year as provided by FDA. The User Fee Cover Sheet (User Fee ID No. 3584) is included with this submission.

Please note that in accordance with the provisions of sections 505 (c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR 314.108 (b)(4), exclusivity is claimed for this product. Information in support of the claim for exclusivity is provided in Section 19 of this application.

In accordance with 314.50(d)(1)(v), we certify that a field copy of this application has been sent to the Newark District Office.

Please be advised that material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

MB/kb
Enclosures

Electronic Submission Information

Description Format (Electronic/Paper)

The following identifies the primary sections included in this submission. Each section has been identified with an "X" if presented in paper or electronically. If a section is not included in this application, it has been removed from this list.

Item	Description	Electronic	Paper
1	Index	X	X
2	Labeling	X	X
3	Application Summary	X	X
4	Chemistry	X	X
5	Nonclinical Pharmacology & Toxicology	X	X
6	Human Pharmacokinetics and Bioavailability	X	X
8	Clinical	X	X
10	Statistical	X*	X
11	Case Report Tabulations	X	
12	Case Report Forms	X	
13	Patent Information	X	X
16	Debarment Certification	X	X
18	User Fee Cover Sheet	X	X
19	Other - Exclusivity Statement	X	X

* This information is identical to Item 8.

Electronic Submission Summary

Media Type:	CD-ROM
Number of Media:	7 - Electronic Submission
	2 - Clinical Data and Supporting Information
	9 - Individual Animal Data
	1 - Requested Documents in Word 97 Format
File Formats:	Portable Document Format (PDF)/ SAS Transport Version 5 Format
Total Size:	Clinical Data/Supporting Information - 933MB
	Electronic Submission - 3.85 GB

Virus Verification

This is to certify that this electronic submission has been scanned for viruses using Intel LANDesk 95, version 5.0.

Sponsor Contacts

Regulatory Affairs Manager:	Michael Belman U.S. Regulatory Affairs (908) 740-4997
Technical Support:	Tracey Blazovic, Associate Director Worldwide Regulatory Affairs (908) 740-4259

Guidance Deviations

EXHIBIT 10

IND CHRONOLOGY FOR ASMANEX® TWISTHALER® PRODUCT

SECOND QUARTER 1993

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering letter requesting intercession on three matters
Letter to FDA	Schering request for pre-IND meeting with FDA in 7/2003 to discuss CMC issues on mometasone furoate dry powder inhalation IND and informing FDA of intent to file IND first quarter 1994

THIRD QUARTER 1993

ACTIVITY/ DOCUMENT TYPE	SUBJECT
PRE-IND Meeting	Meeting to review design and operation of dry powder device and formulation to be used for product, to present proposed testing for release and stability, and to present specifications

FOURTH QUARTER 1993

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering submission of requested sample of format for toxicology section of mometasone dry powder IND
Letter to FDA	Schering letter regarding format for IND and requesting conference call to discuss FDA suggestions on toxicology issues
Letter to FDA	Schering request for pre-IND meeting with FDA pilot drug evaluation staff to discuss Schering's developmental plans for mometasone furoate dry powder
Letter to FDA	Schering letter to clarify several issues regarding the toxicology format for toxicity studies for IND submission

FIRST QUARTER 1994

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering update to 5/14/1993 letter submitting a list of meetings previously requested with the Division

SECOND QUARTER 1994

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering request for pre-IND meeting to discuss the mometasone furoate dry powder IND along with tentative agenda and items for discussion
Letter to FDA	Schering pre-IND meeting package including a proposed agenda and presenters, comprehensive summary of pharmacology, toxicology and pharmacokinetics, and a general investigational plan and request for pre-IND meeting

THIRD QUARTER 1994

ACTIVITY/ DOCUMENT TYPE	SUBJECT
IND Application	Submission of mometasone dry powder inhaler IND
Letter from FDA	FDA acknowledgement letter assigning IND # 46,216 to mometasone furoate dry powder inhaler (DPI) IND

FOURTH QUARTER 1994

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA letter providing comments on Protocol C94-071 and finding protocol safe to proceed and noting FDA has comments regarding DPI development program
Letter to FDA	Schering letter informing FDA that Schering is conducting an investigation of validity of certain mometasone assay after an employee indicated that data had been withheld from

ACTIVITY/ DOCUMENT TYPE	SUBJECT
	management

FIRST QUARTER 1995

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new final protocol
Letter to FDA	Schering submission of additional information documenting actions taken to address concerns regarding enzyme immunoassay (EIA) used to detect plasma levels of mometasone furoate
Letter to FDA	Schering submission of minutes of 2/10/1995 FDA conference call regarding mometasone EIA issues
Letter to FDA	Schering confirmation that EIA issues are confined to mometasone EIA alone and affect only mometasone nasal inhaler, dry powder, and oral inhalers INDs and commitment to forward revised toxicology plan for all mometasone formulations by mid-March
Letter to FDA	Schering submission of revised toxicology plan for all mometasone formulations and request for preclinical toxicology meeting to discuss the program to support all formulations

SECOND QUARTER 1995

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering minutes of 5/17/1995 meeting with FDA to review the extent of overall preclinical toxicology program for all mometasone formulations, including, per FDA request, a list of all completed preclinical studies with date and place of submission
Letter to FDA	Schering Information Amendment: updated bulk substance synthesis and investigator's brochure

THIRD QUARTER 1995

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: updated bulk substance synthesis and investigator's brochure
Letter from FDA	FDA notice of inspection of nonclinical testing facility and audit of sponsor study and request that Schering submit identity and purity of test article for any IND or NDA used for this study
Letter from FDA	FDA minutes and comments on Schering's minutes from 5/17/1995 pre-NDA pharmacology/preclinical meeting with FDA
Letter to FDA	Schering information package in preparation for 8/16/1999 including agenda, overview of preclinical toxicology program, preliminary carcinogenicity study results, and data on metabolism and pharmacokinetics of mometasone furoate
Letter to FDA	Schering Protocol Amendment: New protocol C94-127
Letter to FDA	Schering response to 7/26/1995 request for information regarding P-5836
Letter to FDA	Schering response to a 7/26/1995 request for data describing identity and purity of test article
Letter to FDA	Schering minutes of 8/16/1995 meeting regarding preclinical issues
Letter to FDA	Schering Information Amendment: copies of overheads presented at 8/16/1995 preclinical meeting
Letter to FDA	Schering request for conference call to discuss labeling for dry powder inhalers

FOURTH QUARTER 1995

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA response to 9/16/1995 fax regarding issues related to testing and labeling on dry powder inhalers based on emitted dose
Letter from FDA	FDA letter recommending nomenclature for inhaled and intranasal drug products: proprietary name should include quantitative amount of active ingredient delivered per dose
Letter to FDA	Schering Protocol Amendment: Study protocol C94-127 amended on 8/15/1995 and new investigators

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA letter stating that information in Schering 8/24/1999 letter in response to FDA 7/26/1995 letter satisfies FDA's GMP concerns
Letter to FDA	IND Annual Report
Letter from FDA	FDA chemistry comments on 9/13/1994 original IND pertaining to drug substance, drug product, specifications and test methods, and container and closure
Letter to FDA	Schering Information Amendment: amendment to C94-127 and new investigator added
Letter to FDA	Schering Information Amendment: chem/micro, pharm/tox, clinical and new protocol and new investigator

FIRST QUARTER 1996

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering submission of pre-clinical reports

THIRD QUARTER 1996

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment/Protocol Amendment: revisions to investigators brochure to include mometasone furoate nasal spray phase II/III efficacy and safety data, toxicology studies, phase I dry powder mix 28-day study and phase II pure dry powder study, and updated pharmacology section; new protocols
Letter to FDA	Schering Information Amendment: clinical

FOURTH QUARTER 1996

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new investigator and submission of labeling for study C96-134 and C96-137 and updated CMC section to support use of mometasone furoate dry powder inhaler device delivering alternate strengths per inhalation, vanceril

ACTIVITY/ DOCUMENT TYPE	SUBJECT
	inhaler and placebo
Letter to FDA	Schering Information Amendment: information to support use of Brantford chemicals' methacholine chloride for challenge testing
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering C94-127 study report corrections
Letter to FDA	Schering request for meeting to discuss dry powder inhaler development, specifically CMC data
Letter to FDA	Schering Protocol Amendment: change in protocol
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	IND Annual Report
Letter to FDA	Schering Information Amendment: pharm/tox

FIRST QUARTER 1997

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering submission of in vitro metabolism of SCH 32088 across specifies by liver, lung, and intestinal tissue
Letter to FDA	Schering Information/Protocol Amendment: updated investigator brochure
Letter from FDA	FDA agenda for 2/10/1997 meeting with FDA to discuss DPI device
Letter to FDA	Schering Protocol Amendment: multiple dose safety study of mometasone furoate dry powder inhalation in asthmatic children
Letter to FDA	Schering Protocol Amendment: new protocol and new investigator
Letter to FDA	Schering Protocol Amendment: new protocol and new investigator
Letter to FDA	Schering presentation slide and meeting minutes for 2/10/1997 meeting on development of Schering's dry powder inhaler device

SECOND QUARTER 1997

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: change in protocol and new investigator
Letter to FDA	Schering Protocol Amendment: addition of inspiratory flow rate measurements
Letter to FDA	Schering Protocol Amendment: addition of inspiratory flow rate measurements at four selected sites
Letter to FDA	Schering request for review of Asmanex metercap tradename and investigations site address changes and new investigators
Letter to FDA	Schering 15-Day IND Safety Report: adverse drug reaction

SECOND QUARTER 1997

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering 15-Day IND Safety Report: adverse drug reaction
Letter to FDA	Schering Protocol Amendment: new protocol and new investigator

THIRD QUARTER 1997

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: updated site information
Letter to FDA	Schering Information Amendment: draft protocol on bone metabolism study for comment
Letter to FDA	Schering Information/Protocol Amendment: chem/micro amendment, new protocol, and new investigator
Letter from FDA	FDA facsimile stating "it has been agreed that qualification and identification will remain the same. However, at great or equal to 0.1%, the impurity will need to be specified" in relation to one part process
Letter from FDA	FDA comments regarding draft protocol for bone density study

FOURTH QUARTER 1997

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: chem/micro clinical amendment, new protocol, change in protocol, and new investigator
Letter to FDA	Schering letter regarding change of statistical analysis plan to drop treatment X investigator terms from model for efficacy analyses in several multicenter protocols
Letter from FDA	FDA response regarding the conduct of stability studies on trade package of DPI to apply for sample size without conducting separate stability studies and sample and proposed protocol
Letter to FDA	Schering Information/Protocol Amendment: new protocol and new investigator
Letter to FDA	IND Annual Report

FIRST QUARTER 1998

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: clinical information and new investigator
Letter to FDA	Schering Information/Protocol Amendment: new protocol, new investigator, and clinical information
Letter from FDA	FDA comments regarding Asmanex name
Letter to FDA	Schering letter regarding transfer of obligations to clinical research for certain protocols
Letter to FDA	Schering letter regarding end of phase 2 meeting request and briefing book
Letter from FDA	FDA preliminary attendees for end of phase 2 meeting
Letter to FDA	Schering letter with pre-meeting package for end of phase 2 CMC meeting including items for discussion and background information on drug substance and drug product
Letter to FDA	Schering preliminary reports on C96-0136 and CP96-137 for end of phase two meeting
Letter to FDA	Schering Protocol Amendment: new protocol
Letter to FDA	Schering response to FDA 1/16/1998 facsimile regarding

ACTIVITY/ DOCUMENT TYPE	SUBJECT
	Asmanex name

SECOND QUARTER 1998

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering facsimile of additional information for 4/27/1998 end of phase two pre-NDA CMC meeting
Letter to FDA	Schering Information/Protocol Amendment: clinical information, change in protocol, and new investigator
Letter from FDA	FDA letter listing recommended tests in addition to NF compendial tests for lactose used in dry powder inhaler
Letter from FDA	FDA letter stating that revised statistical analysis plan submitted 10/15/1997 is acceptable and that graphical method on liberal level of significance is recommended for supplementary test of consistency across centers
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering submission of stability protocol for manufacturing sites specific stability batches as discussed and agreed upon during 4/17/1998 meeting
Letter to FDA	Schering Protocol Amendment: site-specific amendments to require discontinuation of patients upon onset of menses
Letter from FDA	FDA list of preliminary attendees for 9/14/1998 pre-NDA meeting and requiring briefing package by 8/14/1998

THIRD QUARTER 1998

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA comments regarding protocols for alternate indications
Letter from FDA	FDA request for re-analysis of samples for major metabolic products and any information available describing efficacy/toxicity of metabolites
Letter to FDA	Schering letter regarding international sites and new sub-investigator
Letter to FDA	Schering electronic proposal reflecting guidance document

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering request for confirmation regarding acceptability of long term safety data in 4 month update for November 1998 NDA
Letter to FDA	Schering Protocol Amendment: new protocol
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering proposal to change the laminate used in the overwrap for the DPI inhaler to a thicker material for optimum machinability
Letter from FDA	FDA's minutes of 4/17/1998 meeting to discuss CMC issues
Letter to FDA	Schering 15-Day IND Safety Report: adverse drug reaction
Letter to FDA	Schering pre-NDA meeting briefing package
Letter to FDA	Schering response to 7/7/1998 letter requesting metabolite information
Letter to FDA	Schering letter of understanding clarifying use of Oneida Research Services for analytical testing of mometasone furoate DPI
Letter to FDA	Schering Information Amendment: per discussion of 9/14/1998 pre-NDA meeting, Schering submission of available stability data on DPI without moisture protective secondary overwrap at 25 degrees Celsius/75% RH storage conditions

FOURTH QUARTER 1998

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new protocol, change in protocol
Letter from FDA	FDA minutes of 9/14/1998 pre-NDA meeting
Letter to FDA	Schering Information/Protocol Amendment: new investigators for international sites, and clinical amendments
Letter to FDA	Schering 15-Day IND Safety Report: adverse drug reaction
Letter to FDA	Schering 15-Day IND Safety Report: adverse drug reaction
Letter from FDA	FDA comments regarding bone density study
Letter to FDA	Schering Protocol Amendment: change in protocol and new investigator
Letter to FDA	Schering Protocol Amendment: new investigator

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering comments on items 1-3 of pre-NDA meeting minutes
Letter to FDA	Schering Protocol Amendment: new protocol and new investigator
Letter to FDA	IND Annual Report
Letter to FDA	Schering proposed study request for alternate indications
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and change in protocol

FIRST QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, change in protocol, and new investigators
Letter to FDA	Schering Information Amendment: revision to include addendum regarding 6-beta-hydroxy metabolite information
Letter to FDA	Schering clinical letter
Letter to FDA	Schering Protocol/Information Amendment: clinical amendment and new investigator
Letter to FDA	Schering Protocol Amendment: new protocol

SECOND QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: change in protocol
Letter to FDA	Schering Information Amendment: CMC information on mometasone furoate dry powder inhalation
Letter to FDA	Schering Protocol Amendment: new protocol and new investigator
Letter to FDA	Schering request for meeting re: program for alternate indication
Letter to FA	Schering Information/Protocol Amendment: clinical amendment and new investigators

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA letter scheduling guidance meeting for alternate indication for 6/22/1999 and requesting briefing packet by 6/8/1999
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and new investigator
Letter to FDA	Schering Information Amendment: alternate indication meeting briefing package with protocol concepts
Letter from FDA	FDA letter advising of combined guidance meeting for MDI PM QD Dosing and DPI alternate indication on 6/22/1999

THIRD QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering GCP audit of Dr. Gary Cohen
Letter to FDA	Schering draft protocols for alternate indication and request for comment on clinical program
Letter to FDA	Schering Information/Protocol Amendment: change in protocol and new investigator
Letter to FDA	Schering Information Amendment: PK information package
Letter to FDA	Schering GCP audit of Gary Cohen
Letter to FDA	Schering Information Amendment: phase I CSRs for alternate indication
Letter to FDA	Schering Protocol Amendment: new protocol and new investigator
Letter from FDA	FDA comments on protocols for alternate indications
Letter to FDA	Schering Protocol Amendment: new protocol, change in protocol, and new investigator
Letter to FDA	Schering letter submitting Asmanex Twisthaler tradename for review

FOURTH QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, change in protocol, and new investigator
Letter to FDA	IND Annual Report
Letter to FDA	Schering Information/Protocol Amendment: protocols for alternate indications, transfers of obligations, and responses to 8/19/1999 letter on draft protocols

FIRST QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Annual Report AE narrative

SECOND QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, and change in protocol

THIRD QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, change in protocol, and new investigator
Letter to FDA	Schering CMC Amendment
Letter to FDA	Schering Protocol Amendment: new investigator

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Protocol Amendment: new investigator

FOURTH QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: chem/micro amendment, new protocol, and new investigator
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, change in protocol, and new investigator
Letter to FDA	Schering Information Amendment: CMC amendment providing for updated specs and methods for alternate strength per inhalation DPI, information to support radioactive 32088 drug substance
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and new investigators
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Information Amendment: revised statistical analysis methods
Letter to FDA	IND Annual Report
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering Protocol Amendment: new protocol and new investigator
Letter to FDA	Schering Information Amendment: clinical amendment

FIRST QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Protocol Amendment: clinical amendment
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and new investigator
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment

ACTIVITY/ DOCUMENT TYPE	SUBJECT
	and new investigator
Letter to FDA	Schering Protocol Amendment: new protocol
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and new investigator
Letter from FDA	FDA protocol comments

SECOND QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and new investigators
Letter to FDA	Schering Protocol Amendment: New protocol and new investigator
Letter to FDA	Schering response to FDA 3/15/1999 letter regarding P01431
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, change in protocol, and new investigators
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, change in protocol, and new investigators
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and new investigators

THIRD QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, and change in protocol
Letter to FDA	Schering Protocol Amendment: new investigator
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment and new investigator
Letter to FDA	Schering Protocol Amendment: new investigator

FOURTH QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information/Protocol Amendment: clinical amendment, change in protocol, new investigators
Letter to FDA	Schering Protocol Amendment: change in protocol
Letter to FDA	Schering Information/Protocol Amendment: pharmacology/toxicology amendment, new investigator
Letter to FDA	Schering desk copy of pre-screening adverse event
Letter to FDA	IND Annual Report
Letter to FDA	Schering Information Amendment: clinical amendment

FIRST QUARTER 2002

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering general correspondence
Letter to FDA	Schering Information Amendment
Letter to FDA	Schering letter regarding IND study, Dr. Scheninberg

SECOND QUARTER 2002

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering request for review and comment on detailed statistical analysis plan
Letter to FDA	Schering Information Amendment: clinical amendment

THIRD QUARTER 2002

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA comment on Asmanex DPI statistical plan
Letter to FDA	Schering Protocol Amendment
Letter to FDA	Schering response to FDA comments on data analysis plan

FOURTH QUARTER 2002

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering 15-Day IND Safety Report
Letter to FDA	IND Annual Report

FIRST QUARTER 2003

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering Information Amendment: CMC amendment

SECOND QUARTER 2003

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering Information Amendment: site updates
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering Information Amendment: clinical amendment

THIRD QUARTER 2003

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering Information Amendment: clinical amendment
Letter to FDA	Schering letter regarding Customs entry 066-1166133-8 and FDA hold
Letter to FDA	Schering monitoring visit reports package to DSI
Letter to FDA	Schering facsimile copy of 7/28/2003 7-day alert
Letter to FDA	Schering 7-Day INDA Safety Report
Letter to FDA	Schering 15-Day IND Safety Report

FOURTH QUARTER 2003

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering 15-Day IND Safety Report
Letter to FDA	IND Annual Report
Letter to FDA	Schering request for pre-sNDA meeting regarding alternate indications
Letter to FDA	Schering request for pre-sNDA meeting regarding alternate strengths and indications

FIRST QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA letter scheduling Asmanex alternate indication pre-sNDA meeting for 2/24/2004
Letter from FDA	FDA letter scheduling Asmanex Twisthaler pre-sNDA meeting for 2/23/2004
Letter to FDA	Schering pre-sNDA meeting briefing information
Letter to FDA	Schering alternate indication pre-sNDA meeting briefing information
Letter from FDA	FDA comments on alternate indication pre-sNDA briefing book
Letter to FDA	Schering end use letter regarding FDA holds
Letter to FDA	Schering letter with requested CRF pages

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA minutes of 2/23/2004 pre-NDA meeting regarding alternate strengths
Letter to FDA	Schering requests for clarification of 2/23/2004 meeting minutes

SECOND QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering end use letter regarding FDA hold
Letter to FDA	Schering end use letter regarding FDA hold

THIRD QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering end use letter regarding FDA hold
Letter to FDA	Schering end use letter regarding FDA hold
Letter to FDA	Schering request for review of study concept and promotional claims

FOURTH QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering end use letter regarding FDA holds
Letter to FDA	Schering updated end use letter regarding FDA holds
Letter from FDA	FDA comments regarding Asmanex vs. Advair study concept
Letter to FDA	IND Annual Report

EXHIBIT 11

NDA CHRONOLOGY FOR ASMANEX® TWISTHALER® PRODUCT

FOURTH QUARTER 1998

ACTIVITY/ DOCUMENT TYPE	SUBJECT
NDA	Schering submission of NDA 21067 for Asmanex® Twisthaler® (mometasone furoate inhalation powder)

FIRST QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering replacement NDA volumes and electronic files
Letter to FDA	Schering NDA Amendment
Letter to FDA	Schering submission of device samples
Letter to FDA	DSI requested CRFs and site information
Letter to FDA	Schering NDA Amendment
Letter to FDA	Schering submission of revised toxicology study summaries
Letter from FDA	FDA written request for alternate indication studies
Letter from FDA	FDA response to proposed alternate indication study request
Letter to FDA	Schering preclinical letter
Letter to FDA	Schering submission of monitoring survey table and SOP
Letter to FDA	Schering NDA amendment to submit samples of device in its moisture protective packaging pouch, equivalency report between different pouch configurations with the configuration on stability and different laminates, and a request for a meeting or teleconference to obtain agreements on outstanding items
Letter to FDA	Schering 4 month safety update, long term safety data, Keto study safety synopsis only

SECOND QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering request for a meeting to discuss issues including identification of the devices, ink-jet coding, preferred pouches and pouch laminate
Letter to FDA	Schering response to 4/7/1999 conference call with Dr. Gebert (FDA) to clarify his requests
Letter from FDA	FDA information request letter based on preliminary review of CMC section of NDA
Letter to FDA	Schering biometrics review aid
Letter to FDA	Schering submission of corrected lab tables and CD Rom for safety update
Letter to FDA	Schering response to biometrics request: analysis of covariance
Letter from FDA	FDA questions regarding lab values and vital sign tables
Letter from FDA	FDA grant of Scherings request for meeting to discuss CMC items; scheduled for 7/15/1999 contingent upon Schering sending the pre-meeting package by 7/1/1999
Letter from FDA	FDA request for clarification of ECGs, subjects 174 and 53
Letter to FDA	Schering NDA Amendment: copy of 6/30/1999 NDA Amendment to 5/4/1999 CMC information request letter
Letter to FDA	Schering NDA Amendment: response to all comments from CMC information request letter. Submission of samples for both strengths and request that in lieu of meeting that FDA provide feedback on questions regarding device coding, identification, and pouching in earlier submissions.

THIRD QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA clinical pharmaceutical/biopharmaceutical questions
Letter to FDA	Schering response to facsimile requesting clarification of ECGs for two subjects
Letter to FDA	Schering submission of revised vital sign tables and body weight tables
Letter from FDA	FDA letter informing Schering of scheduling of pre-approval inspection of Singapore site

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering response to facsimile
Letter from FDA	FDA medical review questions
Letter from FDA	FDA facsimile (1) with comments on NDA Amendment regarding ink jet coding of lot number, alternate pouch/laminate presentation, (2) requesting expiry dating on the device holding the drug; (3) requesting color differentiation between strengths on both label and device, and (4) stability data to support alternate pouch/laminate presentation
Letter to FDA	Schering provision of stability data in excel format on disk
Letter to FDA	Schering response to 8/4/1999 medical reviewer's request
Letter to FDA	Schering request for waiver on importation of SPI from Singapore
Letter from FDA	Formal letter copy of FDA facsimile received on 8/17/1999
Letter to FDA	Schering FDA Amendment: (1) response to 8/17/1999 fax with comments on ink jet coding, alternate laminate material and pouch presentations, (2) response that expiry dating will be stamped on the device, and (3) strength differentiation by color strategy and (4) withdrawal of alternate laminate/powder presentations
Letter from FDA	FDA response to importation waiver request approving waiver of importation of lot of drug product only
Letter to NDA	Schering NDA Amendment: submission of information in response to request for listing of types of devices used in clinical and stability studies

FOURTH QUARTER 1999

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA NDA Approvable Letter
Letter from FDA	FDA request for: (1) whole and broken down version of commercial development device, (2) detailed dimensional drawings for parts that differ between commercial and developmental device, (2) release data for Singapore site specific batches obtained at Singapore before shipment to Kenilworth for enrollment in stability program
Letter to FDA	Schering notification of intent to address approvable letter deficiencies
Letter to FDA	Schering letter to clarify requirement for safety update request in 10/1/1999 letter

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering submission of study report P000-450 and P00-451 and request for comments
Letter to FDA	Schering letter informing that FDA Asmanex® postcard was inadvertently distributed by advertising agency
Letter to FDA	Schering response to 10/1/1999 approvable letter with safety update
Letter to FDA	Schering request for a conference call to discuss protocol concept for study for topical mometasone furoate products and modifications to alternate indication request

FIRST QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA letter acknowledging resubmission of 12/1/1999 and setting user fee goal date of 6/2/2000
Letter to FDA	Schering letter providing additional information regarding 2/28/2000 teleconference: final agenda, list of questions, and proposed revisions to alternate indication request
Letter from FDA	FDA letter outlining CMC deficiencies in NDA Amendments of 6/30/1999, 8/23/1999, 9/17/1999, 10/1/1999, and 12/1/1999 and providing labeling comments from chemistry reviewer.
Letter from FDA	FDA pharmacology and toxicology comments and written record of labeling changes already incorporated in Nasonex labeling
Letter from FDA	FDA response to Schering study concepts
Letter to FDA	Schering NDA Amendment responding to comments of 1/24/2000 letter based on 2/14/2000 meeting with agency
Letter from FDA	Approvable letter, review of 12/1/1999 responses
Letter to FDA	Schering letter regarding intent to amend application to address deficiencies cited in 3/14/2000 approvable letter

SECOND QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA minutes of 2/14/2000 meeting

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering NDA Amendment responding to 3/14/2000 approvable letter with comments on CMC, labeling, and clinical section of NDA and providing responses to all comments

THIRD QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA letter acknowledging receipt of 6/2/2000 responses to 3/14/2000 action letter and informing Schering that responses are complete and setting 12/5/2000 as the user fee goal date
Letter from FDA	FDA CMC deficiency letter based on 6/2/2000 NDA amendment totalling 22 comments (CMC and CMC labeling)
Letter to FDA	Schering letter informing FDA that the responses to 8/10/2000 CMC letter would be submitted on 9/14/2000 and providing additional information on items for discussion at 9/20/2000 meeting
Letter to FDA	Schering submission of word file with 6/2/2000 test, minus revision annotations
Letter to FDA	Schering letter forwarding slides presented at 9/20/2000 meeting with CMC review team

FOURTH QUARTER 2000

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA minutes of 9/20/2000 meeting
Letter to FDA	Schering submission of field copy of NDA Amendment of 10/17/2000
Letter to FDA	Schering response to 8/10/2000 CMC letter including responses to all comments and three commitments
Letter to FDA	Schering submission of updated stability report of up to 24 months on Kenilworth manufactured drug product made from single cavity mold and using RJR laminated pouch
Letter to FDA	Schering package mock-ups with storage condition revised per 10/17/2000 response 21
Letter from FDA	FDA facsimile of biometrics request for SAS format files of stability data and examples of file formats

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA preliminary labeling comments
Letter to FDA	Schering response to 11/16/2000 labeling comments and revised package insert and patient instructions
Letter to FDA	Schering request for written confirmation that written request would be satisfied by fewer patients in the event of reaching a rate-limiting milestone and meeting criteria of safety concerns as stated in 3/17/1999 written request
Letter to FDA	Schering letter regarding intent to amend the NDA as per approvable letter
Letter from FDA	FDA letter acknowledging receipt of revised written request and noting filing date was changed to 9/17/2001

FIRST QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering submission of a CD with requested SAS data sets for stability data (CD submitted with only the review copy)
Letter to FDA	Schering submission for comment of discussion document regarding bulk shipping of MF DPI between manufacturing sites; studies will start after incorporating FDA comments
Letter from FDA	FDA comments on discussion document containing proposal for qualification of bulk protective packaging for storage and transportation of filled inhalers from Singapore manufacturing facility to Kenilworth testing and final packaging facility

SECOND QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering submission of request for changes to mometasone furoate request for alternate indication
Letter to FDA	Schering submission of corrected copies of FDA written request for alternate indication
Letter from FDA	FDA comments on proposed changes to mometasone furoate

THIRD QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA comments on proposed changes to mometasone furoate
Letter to FDA	Schering response to FDA draft of proposed changes for study 2 in written request for alternate indication
Letter to FDA	Schering facsimile of comments on 7/26/2001 FDA proposed revisions to written request for studies for alternate indication
Letter to FDA	Schering official copy of comments on FDA 7/26/2001 draft of revisions to mometasone furoate written request
Letter from FDA	FDA response to Schering's 8/3/2001 facsimile for changes to the alternate indication request deleting criteria for efficacy evaluation
Letter from FDA	FDA minutes of 12/18/2000 meeting to discuss product particle size specification and marketed product stability protocol comments from 12/4/2000 approvable letter
Letter from FDA	FDA acknowledgement of receipt of revised mometasone furoate written request
Letter to FDA	Schering submission of alternate indication study reports and request for alternate indication determination
Letter to FDA	Schering facsimile copy of 9/14/2001 letter requesting exclusivity determination to Office of Generic Drugs

FOURTH QUARTER 2001

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	Approvable letter with CMC and labeling comments
Letter to FDA	Schering letter requesting changes to the minutes of 12/18/2001 meeting

FIRST QUARTER 2002

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering request for revisions to 12/16/2000 meeting minutes

FOURTH QUARTER 2003

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering complete response to 12/4/2000 action letter including 200 mcg ODPM and safety update
Letter to FDA	Schering response to FDA request for individual cascade impaction data
Letter from FDA	FDA acknowledgement of receipt of response to 12/4/2000 action letter

FIRST QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering letter regarding responsible individuals
Letter to FDA	Schering response to FDA request for financial disclosure and SAS files for 200 mcg QD PM studies
Letter from FDA	FDA facsimile requesting resubmission of SAS files sent 2/6/2004
Letter to FDA	Schering resubmission of electronic SAS files for 200 Mcg QDPM and safety update
Letter to FDA	Schering PI file
Letter from FDA	FDA request for information

SECOND QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering letter regarding population requiring alternate strength
Letter from FDA	FDA district status notification
Letter to FDA	AMCOR Flexibles letter of authorization to DMF 2045
Letter from FDA	FDA letter clearing Clarinex syrup for approval after inspection
Letter from FDA	FDA comments on PI, patient instructions, and packaging
Letter to FDA	Schering copy of letter to FDA from AMCOR Flexibles correcting a typographical error in their DMF 2045

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering revised draft labeling
Letter from FDA	FDA approvable letter
Letter to FDA	Schering notification of intent to amend
Letter to FDA	FDA draft proposal to revise specifications for particle size distribution by Canada Impaction
Letter to FDA	Schering complete response to 5/17/2004 action letter
Letter to FDA	Schering proposed specifications for particle size distribution by Cascade Impaction/proposal for metered dose testing

THIRD QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA minutes of 6/18/2004 meeting regarding draft proposal to revise specifications
Letter from FDA	FDA acknowledgement of Schering response to 5/17/2004 approvable letter
Letter to FDA	Schering response to 6/29/2004 submission
Letter to FDA	Complete response to 5/17/2004 action letter

FOURTH QUARTER 2004

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering end use letter for entry 066-1178641-6
Letter to FDA	Schering response to FDA request for information
Letter to FDA	Schering response to FDA request regarding draft labeling
Letter from FDA	FDA Asmanex CMC discipline review letter
letter to FDA	Schering complete response to CMC discipline review letter

FIRST QUARTER 2005

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter from FDA	FDA request for information
Letter to FDA	Schering complete response to request for CMC agreements
Letter from FDA	FDA comments regarding PI and PPI
Letter from FDA	Approval letter

SECOND QUARTER 2005

ACTIVITY/ DOCUMENT TYPE	SUBJECT
Letter to FDA	Schering letter regarding time sensitive patent information
Letter to FDA	Schering NDA 15-day alert
Letter to FDA	Schering letter to DDMAC for pre-clearance of promotional materials

PTO/SB/81 (04-05)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	Patent No.: 5,829,434
Filing Date	Issued: November 3, 1998
First Named Inventor	Thomas J. Ambrosio
Title	INHALER FOR POWDERED MEDICATIONS
Art Unit	3735
Examiner Name	V. Srivastava
Attorney Docket No.	025444.90400

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

[X] Practitioners associated with the Customer Number: 26853

OR

[ ] Practitioner(s) named below:

Name	Registration Number	Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

[X] The address associated with the above-mentioned Customer Number:

OR

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name: Covington & Burling

Address	1201 Pennsylvania Avenue, NW				
City	Washington	State	D.C.	Zip	20004-2401
Country	USA	Telephone	202.662.6000	Email	

I am the:

[ ] Applicant/Inventor.

[X] Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature	[signature]	Date	5/27/05
Name	VP- Patent Law	Telephone	908-298-2306
Title and Company	Henry Hadad - , Schering Corporation		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[ ] *Total of 1 forms are submitted.

PTO/SB/96 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Thomas J. Ambrosio et al.

Application No./Patent No.: 5,829,434 Filed/Issue Date: November 3, 1998

Entitled: INHALER FOR POWDERED MEDICATIONS

Schering Corporation (Name of Assignee), a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [x] the assignee of the entire right, title, and interest; or
2. [ ] an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

in the patent application/patent identified above by virtue of either:

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 007655, Frame 0784, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — 5/27/05 Date

Henry Hadad
Printed or Typed Name — 908-298-2906 Telephone Number

VP- Patent Law
Title